PA NT COOPERATION TREAT

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

MORROW, Joy, D.
Smart & Biggar
900-55 Metcalfe Street
P.O. Box 2999
Station D
Ottawa, Ontario K1P 5Y6
CANADA

Date of mailing (day/month/year)
20 March 2001 (20.03.01)

Applicant's or agent's file reference
77813-1

IMPORTANT NOTIFICATION

International application No.
PCT/CA99/00992

International filing date (day/month/year)
28 October 1999 (28.10.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
MURDIN, Andrew, D.
146 Rhodes Circle
Newmarket, Ontario L3X 1V2
Canada

State of Nationality: CA
State of Residence: CA
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
MURDIN, Andrew, D.
11 Forest Hill Drive
Richmond Hill, Ontario L4B 3C2
Canada

State of Nationality: CA
State of Residence: CA
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Athina Nickitas-Etienne

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

003908655

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

MORROW, Joy, D.
Smart & Biggar
900-55 Metcalfe Street
P.O. Box 2999
Station D
Ottawa, Ontario K1P 5Y6
CANADA

Date of mailing (day/month/year)
20 March 2001 (20.03.01)

Applicant's or agent's file reference
77813-1

IMPORTANT NOTIFICATION

International application No.
PCT/CA99/00992

International filing date (day/month/year)
28 October 1999 (28.10.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
WANG, Joe
48 29th Street
Etobicoke, Ontario M8W 3A8
Canada

State of Nationality: CA
State of Residence: CA
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
WANG, Joe
51 Aspenwood Drive
Toronto, Ontario M2H 2E8
Canada

State of Nationality: CA
State of Residence: CA
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Athina Nickitas-Etienne

Telephone No.: (41-22) 338.83.38

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 August 2000 (17.08.00)	
International application No. PCT/CA99/00992	**Applicant's or agent's file reference** 77813-1
International filing date (day/month/year) 28 October 1999 (28.10.99)	**Priority date** (day/month/year) 28 October 1998 (28.10.98)
Applicant MURDIN, Andrew, D. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 May 2000 (26.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

MORROW, Joy, D.
Smart & Biggar
900-55 Metcalfe Street
P.O. Box 2999
Station D
Ottawa, Ontario K1P 5Y6
CANADA

Date of mailing (day/month/year)
08 November 2000 (08.11.00)

Applicant's or agent's file reference
77813-1

IMPORTANT NOTIFICATION

International application No.
PCT/CA99/00992

International filing date (day/month/year)
28 October 1999 (28.10.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent. [ ] the common representative

Name and Address
CONNAUGHT LABORATORIES LIMITED
1755 Steeles Avenue West
Toronto, Ontario M2R 3T4
Canada

State of Nationality: CA
State of Residence: CA
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
AVENTIS PASTEUR LIMITED
1755 Steeles Avenue West
Toronto, Ontario M2R 3T4
Canada

State of Nationality: CA
State of Residence: CA
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Jean-Marie McAdams

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
77813-1		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/00992	28/10/1999	28/10/1998
Applicant		
CONNAUGHT LABORATORIES LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readble form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/00992

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 24 (all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 1 and 2 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 27 and 28. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide . Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

2. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 3 and 4 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 29. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide . Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

3. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 5 and 6 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 30. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide . Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

4. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 7 and 8 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 31. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide . Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

5. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 9 and 10 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 32. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide. Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

6. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 11 and 12 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 33 and 34. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide. Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which

make use of the nucleic acid, the polypeptide or the antibody.

7. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 13 and 14 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 35 and 36. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide. Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

8. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 15 and 16 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 37. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide. Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

9. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 17 and 18 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 38 and 39. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide. Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under

stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

10. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 19 and 20 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 40 and 41. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide. Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

11. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 21 and 22 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 42. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide. Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

12. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 23 and 24 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 43. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide. Unicellular host transformed with the nucleic

acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

13. Claims: 1-24 (all partially)

A nucleic acid molecule comprising a nucleic acid sequence as shown in SEQ ID NO: 25 and 26 which encodes a polypeptide having an amino acid sequence as shown in SEQ ID NO: 44 and 45. Encoded polypeptide, immunogenic fragment thereof and antibody directed thereto. Fusion polypeptide comprising said polypeptide. Modified polypeptide having improved immunogenicity. Vaccine, pharmaceutical composition and diagnostic kit comprising said nucleic acid sequence or polypeptide. Unicellular host transformed with the nucleic acid. Method for producing the polypeptide by culturing said host. Nucleic acid probe and primer which hybridize under stringent conditions to the nucleic molecule. Methods for preventing, treating or diagnosing Chlamydia infection which make use of the nucleic acid, the polypeptide or the antibody.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]CA 99/00992

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/62 C07K14/295 C07K16/12 A61K39/118 G01N33/53
C12Q1/68 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PEREZ MELGOSA M ET AL: "OUTER MEMBRANE COMPLEX PROTEINS OF CHLAMYDIA PNEUMONIAE" FEMS MICROBIOLOGY LETTERS,NL,AMSTERDAM, vol. 112, no. 2, 1 September 1993 (1993-09-01), pages 199-204, XP002057607 ISSN: 0378-1097 the whole document ---	16,21
P,X	WO 98 58953 A (MADSEN ANNA SOFIE ;BIRKELUND SVEND (DK); KNUDSEN KATRINE (DK); MYG) 30 December 1998 (1998-12-30) page 5, line 24 -page 21, line 29 pages 49-22, SEQ ID NO: 7 and 8; pages 83-88, SEQ ID NO: 29 and 30 --- -/--	1-24

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2000	03. 07. 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kaas, V

4

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 27105 A (GRIFFAIS REMY ;GENSET (FR)) 3 June 1999 (1999-06-03) page 5, line 10 -page 18, line 34 page 46, line 4 -page 47, line 13 page 51, line 6 -page 54, line 30 page 59, line 34 -page 61, line 22 page 63, line 18 -page 66, line 3 page 68, line 36 -page 73, line 31 pages 291-611, SEQ ID NO:1; pages 630-631 ---	1-24
A	WIEDMANN-AL-AHMAD, M.: "Reactions of polyclonal and neutralizing anti-p54 monoclonal antibodies with an isolated, species-specific 54-kilodalton protein of Chlamydia pneumoniae" CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, vol. 4, no. 6, November 1997 (1997-11), page 700-704 XP002132124 cited in the application the whole document ---	1-24
A	ILJIMA, Y.: "Characterization of Chlamydia pneumoniae species-specific proteins immunodominant in humans" JOURNAL OF CLINICAL MICROBIOLOGY, vol. 32, no. 3, March 1994 (1994-03), page 583-588 XP000881638 the whole document -----	1-24

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
[redacted]CA 99/00992

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9858953 A	30-12-1998	AU 8011998 A	04-01-1999
		EP 1007685 A	14-06-2000
WO 9927105 A	03-06-1999	AU 1170299 A	15-06-1999

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07K 14/00

A2

(11) International Publication Number: WO 00/24765

(43) International Publication Date: 4 May 2000 (04.05.00)

(21) International Application Number: PCT/CA99/00992

(22) International Filing Date: 28 October 1999 (28.10.99)

(30) Priority Data:

60/106,034	28 October 1998 (28.10.98)	US
60/106,044	28 October 1998 (28.10.98)	US
60/106,039	28 October 1998 (28.10.98)	US
60/106,042	28 October 1998 (28.10.98)	US
60/106,087	29 October 1998 (29.10.98)	US
60/106,072	29 October 1998 (29.10.98)	US
60/106,073	29 October 1998 (29.10.98)	US
60/106,074	29 October 1998 (29.10.98)	US
60/106,589	2 November 1998 (02.11.98)	US
60/107,034	2 November 1998 (02.11.98)	US
60/107,035	2 November 1998 (02.11.98)	US
60/106,587	2 November 1998 (02.11.98)	US
60/106,588	2 November 1998 (02.11.98)	US

(71) Applicant *(for all designated States except US)*: CONNAUGHT LABORATORIES LIMITED [CA/CA]; 1755 Steeles Avenue West, Toronto, Ontario M2R 3T4 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MURDIN, Andrew, D. [CA/CA]; 146 Rhodes Circle, Newmarket, Ontario L3X 1V2 (CA). OOMEN, Raymond, P. [CA/CA]; RR No. 1, Schomberg, Ontario L0G 1T0 (CA). WANG, Joe [CA/CA]; 48 29th Street, Etobicoke, Ontario M8W 3A8 (CA).

(74) Agents: MORROW, Joy, D. et al.; Smart & Biggar, 900–55 Metcalfe Street, P.O. Box 2999, Station D, Ottawa, Ontario K1P 5Y6 (CA).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: *CHLAMYDIA* ANTIGENES AND CORRESPONDING DNA FRAGMENTS AND USES THEREOF

(57) Abstract

The present invention provides purified and isolated polynucleotide molecules that encode *Chlamydia* polypeptides which can be used in methods to prevent, treat, and diagnose *Chlamydia* infection. In one form of the invention, the polynucleotide molecules are selected from DNA that encode polypeptides CPN100397 (SEQ ID Nos: 1 and 2), CPN100421 (SEQ ID Nos: 3 and 4), CPN100422 (SEQ ID Nos: 4 and 6), CPN100424 (SEQ ID Nos: 7 and 8), CPN100426 (SEQ ID Nos: 9 and 10), CPN100508 (SEQ ID Nos: 11 and 12), CPN100515 (SEQ ID Nos: 13 and 14), CPN100538 (SEQ ID Nos: 15 and 16), CPN100557 (SEQ ID Nos: 17 and 18), CPN100622 (SEQ ID Nos: 19 and 20), CPN100626 (SEQ ID Nos: 21 and 22), CPN100628 (SEQ ID Nos: 23 and 24) and CPN100630 (SEQ ID Nos: 25 and 26).

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BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TITLE OF INVENTION

CHLAMYDIA ANTIGENS AND CORRESPONDING DNA FRAGMENTS AND USES THEREOF

REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/106034, filed October 28, 1998, U.S. Provisional Application No.60/106039, filed October 28, 1998,U.S. Provisional Application No. 60/106042, filed October 28, 1998, U.S. Provisional Application No. 60/106044, filed October 28, 1998, U.S. Provisional Application No. 60/106072, filed October 29, 1998, U.S. Provisional Application No. 60/106073, filed October 29, 1998, U.S. Provisional Application No. 60/106074, filed October 29, 1998,U.S. Provisional Application No. 60/106087, filed October 29, 1998, U.S. Provisional Application No. 60/106587, filed November 2, 1998, U.S. Provisional Application No. 60/106588, filed November 2, 1998, U.S. Provisional Application No. 60/107089, filed November 2, 1998, U.S. Provisional Application No. 60/107034, filed November 2, 1998 and U.S. Provisional Application No. 60/107035, filed November 2, 1998.

FIELD OF INVENTION

The present invention relates to *Chlamydia* antigens and corresponding DNA molecules, which can be used to prevent and treat *Chlamydia* infection in mammals, such as humans.

BACKGROUND OF THE INVENTION

Chlamydiae are prokaryotes. They exhibit morphologic and structural similarities to gram-negative bacteria including a trilaminar outer membrane, which contains lipopolysaccharide and several membrane proteins that are structurally and functionally analogous to proteins found in *E coli*. They are obligate intra-cellular parasites with a unique biphasic life

cycle consisting of a metabolically inactive but infectious extracellular stage and a replicating but non-infectious intracellular stage. The replicative stage of the life-cycle takes place within a membrane-bound inclusion which sequesters the bacteria away from the cytoplasm of the infected host cell.

C. pneumoniae is a common human pathogen, originally described as the TWAR strain of *Chlamydia psittaci* but subsequently recognised to be a new species. *C. pneumoniae* is antigenically, genetically and morphologically distinct from other chlamydia species (*C. trachomatis, C. pecorum* and *C. psittaci*). It shows 10% or less DNA sequence homology with either of *C.trachomatis* or *C.psittaci*.

C. pneumoniae is a common cause of community acquired pneumonia, only less frequent than *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* (Grayston *et al.* (1995) Journal of Infectious Diseases 168:1231; Campos *et al.* (1995) Investigation of Ophthalmology and Visual Science 36:1477). It can also cause upper respiratory tract symptoms and disease, including bronchitis and sinusitis (Grayston *et al.* (1995) Journal of Infectious Diseases 168:1231; Grayston *et al* (1990) Journal of Infectious Diseases 161:618; Marrie (1993) Clinical Infectious Diseases. 18:501; Wang *et al* (1986) Chlamydial infections). Cambridge University Press, Cambridge. p. 329The great majority of the adult population (over 60%) has antibodies to *C. pneumoniae* (Wang *et al* (1986) Chlamydial infections. Cambridge University Press, Cambridge. p. 329), indicating past infection which was unrecognized or asymptomatic.

C. pneumoniae infection usually presents as an acute respiratory disease (*i.e.*, cough, sore throat, hoarseness, and fever; abnormal chest sounds on auscultation). For most patients, the cough persists for 2 to 6 weeks, and recovery is slow. In approximately 10% of these cases, upper respiratory tract infection is followed by bronchitis or pneumonia. Furthermore, during a *C. pneumoniae* epidemic, subsequent

co-infection with pneumococcus has been noted in about half of these pneumonia patients, particularly in the infirm and the elderly. As noted above, there is more and more evidence that *C. pneumoniae* infection is also linked to diseases other than respiratory infections.

The reservoir for the organism is presumably people. In contrast to *C. psittaci* infections, there is no known bird or animal reservoir. Transmission has not been clearly defined. It may result from direct contact with secretions, from fomites, or from airborne spread. There is a long incubation period, which may last for many months. Based on analysis of epidemics, *C. pneumoniae* appears to spread slowly through a population (case-to-case interval averaging 30 days) because infected persons are inefficient transmitters of the organism. Susceptibility to *C. pneumoniae* is universal. Reinfections occur during adulthood, following the primary infection as a child. *C. pneumoniae* appears to be an endemic disease throughout the world, noteworthy for superimposed intervals of increased incidence (epidemics) that persist for 2 to 3 years. *C.trachomatis* infection does not confer cross-immunity to *C. pneumoniae*. Infections are easily treated with oral antibiotics, tetracycline or erythromycin (2 g/d, for at least 10 to 14 d). A recently developed drug, azithromycin, is highly effective as a single-dose therapy against chlamydial infections.

In most instances, *C. pneumoniae* infection is often mild and without complications, and up to 90% of infections are subacute or unrecognized. Among children in industrialized countries, infections have been thought to be rare up to the age of 5 y, although a recent study (E Normann *et al*, Chlamydia pneumoniae in children with acute respiratory tract infections, Acta Paediatrica, 1998, Vol 87, Iss 1, pp 23-27) has reported that many children in this age group show PCR evidence of infection despite being seronegative, and estimates a prevalence of 17-19% in 2-4 y olds. In developing countries, the

seroprevalence of *C. pneumoniae* antibodies among young children is elevated, and there are suspicions that *C. pneumoniae* may be an important cause of acute lower respiratory tract disease and mortality for infants and children in tropical regions of the world.

From seroprevalence studies and studies of local epidemics, the initial *C. pneumoniae* infection usually happens between the ages of 5 and 20 y. In the USA, for example, there are estimated to be 30,000 cases of childhood pneumonia each year caused by *C. pneumoniae*. Infections may cluster among groups of children or young adults (*e.g.*, school pupils or military conscripts).

C. pneumoniae causes 10 to 25% of community-acquired lower respiratory tract infections (as reported from Sweden, Italy, Finland, and the USA). During an epidemic, *C. pneumonia* infection may account for 50 to 60% of the cases of pneumonia. During these periods, also, more episodes of mixed infections with *S. pneumoniae* have been reported.

Reinfection during adulthood is common; the clinical presentation tends to be milder. Based on population seroprevalence studies, there tends to be increased exposure with age, which is particularly evident among men. Some investigators have speculated that a persistent, asymptomatic *C. pneumoniae* infection state is common.

In adults of middle age or older, *C. pneumoniae* infection may progress to chronic bronchitis and sinusitis. A study in the USA revealed that the incidence of pneumonia caused by *C. pneumoniae* in persons younger than 60 years is 1 case per 1,000 persons per year; but in the elderly, the disease incidence rose three-fold. *C. pneumoniae* infection rarely leads to hospitalization, except in patients with an underlying illness.

Of considerable importance is the association of atherosclerosis and *C. pneumoniae* infection. There are several

epidemiological studies showing a correlation of previous infections with *C. pneumoniae* and heart attacks, coronary artery and carotid artery disease (Saikku *et al.*(1988) Lancet;ii:983; Thom *et al.* (1992) JAMA 268:68; Linnanmaki *et al.* (1993), Circulation 87:1030; Saikku *et al.* (1992)Annals Internal Medicine 116:273; Melnick *et al*(1993) American Journal of Medicine 95:499). Moreover, the organisms has been detected in atheromas and fatty streaks of the coronary, carotid, peripheral arteries and aorta (Shor *et al.* (1992) South African. Medical Journal 82:158; Kuo *et al.* (1993) Journal of Infectious Diseases 167:841; Kuo *et al.* (1993) Arteriosclerosis and Thrombosis 13:1500; Campbell *et al* (1995) Journal of Infectious Diseases 172:585; Chiu *et al.* Circulation, 1997 (In Press)). Viable *C. pneumoniae* has been recovered from the coronary and carotid artery (Ramirez *et al* (1996) Annals of Internal Medicine 125:979; Jackson *et al.* Abst. K121, p272, 36th ICAAC, 15-18 Sept. 1996, New Orleans). Furthermore, it has been shown that *C. pneumoniae* can induce changes of atherosclerosis in a rabbit model (Fong *et al* (1997) Journal of Clinical Microbiology 35:48). Taken together, these results indicate that it is highly probable that *C. pneumoniae* can cause atherosclerosis in humans, though the epidemiological importance of chlamydial atherosclerosis remains to be demonstrated.

A number of recent studies have also indicated an association between *C. pneumoniae* infection and asthma. Infection has been linked to wheezing, asthmatic bronchitis, adult-onset asthma and acute exacerbations of asthma in adults, and small-scale studies have shown that prolonged antibiotic treatment was effective at greatly reducing the severity of the disease in some individuals (Hahn DL, *et al.* Evidence for Chlamydia pneumoniae infection in steroid-dependent asthma. Ann Allergy Asthma Immunol. 1998 Jan; 80(1): 45-49.; Hahn DL, *et al.* Association of Chlamydia pneumoniae IgA antibodies with recently symptomatic asthma. Epidemiol Infect. 1996 Dec;

117(3): 513-517; Bjornsson E, *et al.* Serology of chlamydia in relation to asthma and bronchial hyperresponsiveness. Scand J Infect Dis. 1996; 28(1): 63-69.; Hahn DL. Treatment of *Chlamydia pneumoniae* infection in adult asthma: a before-after trial. J Fam Pract. 1995 Oct; 41(4): 345-351.; Allegra L, *et al.* Acute exacerbations of asthma in adults: role of Chlamydia pneumoniae infection. Eur Respir J. 1994 Dec; 7(12): 2165-2168.; Hahn DL, *et al.* Association of Chlamydia pneumoniae (strain TWAR) infection with wheezing, asthmatic bronchitis, and adult-onset asthma. JAMA. 1991 Jul 10; 266(2): 225-230).

In light of these results a protective vaccine against *C. pneumoniae* infection would be of considerable importance. There is not yet an effective vaccine for any human chlamydial infection. It is conceivable that an effective vaccine can be developed using physically or chemically inactivated Chlamydiae. However, such a vaccine does not have a high margin of safety. In general, safer vaccines are made by genetically manipulating the organism by attenuation or by recombinant means. Accordingly, a major obstacle in creating an effective and safe vaccine against human chlamydial infection has been the paucity of genetic information regarding Chlamydia, specifically *C. pneumoniae*.

Studies with *C. trachomatis* and *C. psittaci* indicate that safe and effective vaccine against Chlamydia is an attainable goal. For example, mice which have recovered from a lung infection with *C. trachomatis* are protected from infertility induced by a subsequent vaginal challenge (Pal *et al.*(1996) Infection and Immunity.64:5341). Similarly, sheep immunized with inactivated *C. psittaci* were protected from subsequent chlamydial-induced abortions and stillbirths (Jones *et al.* (1995) Vaccine 13:715). Protection from chlamydial infections has been associated with Th1 immune responses, particularly the induction of INFg - producing CD4+T-cells (Igietsemes *et al.* (1993) Immunology 5:317). The adoptive

transfer of CD4+ cell lines or clones to nude or SCID mice conferred protection from challenge or cleared chronic disease (Igietseme *et al* (1993) Regional Immunology 5:317; Magee *et al* (1993) Regional Immunology 5: 305), and *in vivo* depletion of CD4+ T cells exacerbated disease post-challenge (Landers *et al* (1991) Infection & Immunity 59:3774; Magee *et al* (1995) Infection & Immunity 63:516). However, the presence of sufficiently high titres of neutralising antibody at mucosal surfaces can also exert a protective effect (Cotter *et al.* (1995) Infection and Immunity 63:4704).

Antigenic variation within the species *C. pneumoniae* is not well documented due to insufficient genetic information, though variation is expected to exist based on *C. trachomatis*. Serovars of *C. trachomatis* are defined on the basis of antigenic variation in MOMP, but published *C. pneumoniae* MOMP gene sequences show no variation between several diverse isolates of the organism (Campbell *et al* (1990) Infection and Immunity 58:93; McCafferty *et al* (1995) Infection and Immunity 63:2387-9; Knudsen *et al* (1996) Third Meeting of the European Society for Chlamydia Research, Vienna). Regions of the protein known to be conserved in other chlamydial MOMPs are conserved in *C. pneumoniae* (Campbell *et al* (1990) Infection and Immunity 58:93; McCafferty *et al* (1995) Infection and Immunity 63:2387-9). One study has described a strain of *C. pneumoniae* with a MOMP of greater that usual molecular weight, but the gene for this has not been sequenced (Grayston *et al.* (1995) Journal of Infectious Diseases 168:1231). Partial sequences of outer membrane protein 2 from nine diverse isolates were also found to be invariant (Ramirez *et al* (1996) Annals of Internal Medicine 125:979). The genes for HSP60 and HSP70 show little variation from other chlamydial species, as would be expected. The gene encoding a 76kDa antigen has been cloned from a single strain of *C. pneumoniae*. It has no significant similarity with other known

chlamydial genes (Marrie (1993) Clinical Infectious Diseases. 18:501).

Many antigens recognised by immune sera to *C. pneumoniae* are conserved across all chlamydiae, but 98kDa, 76 kDa and 54 kDa proteins appear to be *C. pneumoniae*-specific (Ref Campos *et al.* (1995) Investigation of Ophthalmology and Visual Science 36:1477; Marrie (1993) Clinical Infectious Diseases. 18:501; Wiedmann-Al-Ahmad M, *et al.* Reactions of polyclonal and neutralizing anti-p54 monoclonal antibodies with an isolated, species-specific 54-kilodalton protein of Chlamydia pneumoniae. Clin Diagn Lab Immunol. 1997 Nov; 4(6): 700-704). Immunoblotting of isolates with sera from patients does show variation of blotting patterns between isolates, indicating that serotypes *C. pneumoniae* may exist (Ref 1,16). However, the results are potentially confounded by the infection status of the patients, since immunoblot profiles of a patient's sera change with time post-infection. An assessment of the number and relative frequency of any serotypes, and the defining antigens, is not yet possible.

Accordingly, a need exists for identifying and isolating polynucleotide sequences of *C. pneumoniae* for use in preventing and treating Chlamydia infection.

SUMMARY OF THE INVENTION

The present invention provides purified and isolated polynucleotide molecules that encode *Chlamydia* polypeptides which can be used in methods to prevent, treat, and diagnose *Chlamydia* infection. In one form of the invention, the polynucleotide molecules are selected from DNA that encode polypeptides CPN100397 (SEQ ID Nos: 1 and 2), CPN100421 (SEQ ID Nos: 3 and 4), CPN100422 (SEQ ID Nos: 5 and 6), CPN100424 (SEQ ID Nos: 7 and 8), CPN100426 (SEQ ID Nos: 9 and 10), CPN100508 (SEQ ID Nos: 11 and 12), CPN100515 (SEQ ID Nos: 13 and 14), CPN100538 (SEQ ID Nos: 15 and 16), CPN100557 (SEQ ID Nos: 17 and

18), CPN100622 (SEQ ID Nos: 19 and 20), CPN100626 (SEQ ID Nos: 21 and, 22), CPN100628 (SEQ ID Nos: 23 and 24) and CPN100630 (SEQ ID Nos: 25 and 26).

Another form of the invention provides polypeptides corresponding to the isolated DNA molecules. The amino acid sequences of the corresponding encoded polypeptides are shown for CPN100397 as SEQ ID Nos: 27 and 28, CPN100421 as SEQ ID No: 29, CPN100422 as SEQ ID No: 30, CPN100424 as SEQ ID No: 31, CPN100426 as SEQ ID No: 32, CPN100508 as SEQ ID Nos: 33 and 34, CPN100515 as SEQ ID Nos: 35 and 36, CPN100538 as SEQ ID No: 37, CPN100557 as SEQ ID Nos: 38 and 39, CPN100622 as SEQ ID Nos: 40 and 41, CPN100626 as SEQ ID No: 42, CPN100628 as SEQ ID No: 43 and CPN100630 as SEQ ID Nos: 44 and 45.

Those skilled in the art will readily understand that the invention, having provided the polynucleotide sequences encoding *Chlamydia* polypeptides, also provides polynucleotides encoding fragments derived from such peptides. Moreover, the invention is understood to provide mutants and derivatives of such polypeptides and fragments derived therefrom, which result from the addition, deletion, or substitution of non-essential amino acids as described herein. Those skilled in the art would also readily understand that the invention, having provided the polynucleotide sequences encoding Chlamydia polypeptides, further provides monospecific antibodies that specifically bind to such polypeptides

The present invention has wide application and includes expression cassettes, vectors, and cells transformed or transfected with the polynucleotides of the invention. Accordingly, the present invention further provides (i) a method for producing a polypeptide of the invention in a recombinant host system and related expression cassettes, vectors, and transformed or transfected cells; (ii) a vaccine, or a live vaccine vector such as a pox virus, *Salmonella typhimurium*, or *Vibrio cholerae* vector, containing a polynucleotide of the

invention, such vaccines and vaccine vectors being useful for, *e.g.*, preventing and treating *Chlamydia* infection, in combination with a diluent or carrier, and related pharmaceutical compositions and associated therapeutic and/or prophylactic methods; (iii) a therapeutic and/or prophylactic use of an RNA or DNA molecule of the invention, either in a naked form or formulated with a delivery vehicle, a polypeptide or combination of polypeptides, or a monospecific antibody of the invention, and related pharmaceutical compositions; (iv) a method for diagnosing the presence of *Chlamydia* in a biological sample, which can involve the use of a DNA or RNA molecule, a monospecific antibody, or a polypeptide of the invention; and (v) a method for purifying a polypeptide of the invention by antibody-based affinity chromatography.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be further understood from the following description with reference to the drawings, in which:

Figure 1 shows the nucleotide sequence of the CPN100397 (SEQ ID No: 1 - entire sequence and SEQ ID No: 2 - coding sequence) and the deduced amino acid sequence of the CPN100397 protein from *Chlamydia pneumoniae* (SEQ ID No: 27 and 28).

Figure 2 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100397 gene.

Figure 3 shows the nucleotide sequence of the CPN100421 (SEQ ID No: 3 - entire sequence and SEQ ID No: 4 - coding sequence) and the deduced amino acid sequence of the CPN100421 protein from *Chlamydia pneumoniae* (SEQ ID No: 29).

Figure 4 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100421 gene.

Figure 5 shows the nucleotide sequence of the CPN100422 (SEQ ID No: 5 - entire sequence and SEQ ID No: 6 - coding sequence) and the deduced amino acid sequence of the CPN100422 protein from *Chlamydia pneumoniae* (SEQ ID No: 30).

Figure 6 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100422 gene.

Figure 7 shows the nucleotide sequence of the CPN100424 (SEQ ID No: 7 - entire sequence and SEQ ID No: 8 - coding sequence) and the deduced amino acid sequence of the CPN100424 protein from *Chlamydia pneumoniae* (SEQ ID No: 31).

Figure 8 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100424 gene.

Figure 9 shows the nucleotide sequence of the CPN100426 (SEQ ID No: 9 - entire sequence and SEQ ID No: 10 - coding sequence) and the deduced amino acid sequence of the CPN100426 protein from *Chlamydia pneumoniae* (SEQ ID No: 32).

Figure 10 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100426 gene.

Figure 11 shows the nucleotide sequence of the CPN100508 (SEQ ID No: 11 - entire sequence and SEQ ID No: 12 - coding sequence) and the deduced amino acid sequence of the CPN100508protein from *Chlamydia pneumoniae* (SEQ ID No: 33 - full length sequence and SEQ ID No: 34 - processed sequence).

Figure 12 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100508 gene.

Figure 13 shows the nucleotide sequence of the CPN100515 (SEQ ID No: 13 - entire sequence and SEQ ID No: 14 - coding sequence) and the deduced amino acid sequence of the CPN100515 protein from *Chlamydia pneumoniae* (SEQ ID No: 35 - full length sequence and SEQ ID No: 36 - processed sequence).

Figure 14 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100515 gene.

Figure 15 shows the nucleotide sequence of the CPN100538 (SEQ ID No: 15 - entire sequence and SEQ ID No: 16 - coding sequence) and the deduced amino acid sequence of the CPN100538 protein from *Chlamydia pneumoniae* (SEQ ID No: 37).

Figure 16 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100538 gene.

Figure 17 shows the nucleotide sequence of the CPN100557 (SEQ ID No: 17 - entire sequence and SEQ ID No: 18 - coding sequence) and the deduced amino acid sequence of the CPN100557 protein from *Chlamydia pneumoniae* (SEQ ID No: 38 - full length sequence and SEQ ID No: 39 - processed sequence).

Figure 18 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100557 gene.

Figure 19 shows the nucleotide sequence of the CPN100622 (SEQ ID No: 19 - entire sequence and SEQ ID No: 20 - coding sequence) and the deduced amino acid sequence of the CPN100622 protein from *Chlamydia pneumoniae* (SEQ ID No: 40 - full length sequence and SEQ ID No: 41 - processed sequence).

Figure 20 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100622 gene.

Figure 21 shows the nucleotide sequence of the CPN100626 (SEQ ID No: 21 - entire sequence and SEQ ID No: 22 - coding sequence) and the deduced amino acid sequence of the CPN100626 protein from *Chlamydia pneumoniae* (SEQ ID No: 42).

Figure 22 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100626 gene.

Figure 23 shows the nucleotide sequence of the CPN100628 (SEQ ID No: 23 - entire sequence and SEQ ID No: 24 - coding sequence) and the deduced amino acid sequence of the CPN100628 protein from *Chlamydia pneumoniae* (SEQ ID No: 43).

Figure 24 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100628 gene.

Figure 25 shows the nucleotide sequence of the CPN100630 (SEQ ID No: 25 - entire sequence and SEQ ID No: 26 - coding sequence) and the deduced amino acid sequence of the CPN100630 protein from *Chlamydia pneumoniae* (SEQ ID No: 44 - full length sequence and SEQ ID No: 45 - processed sequence).

Figure 26 shows the restriction enzyme analysis of the gene encoding the *C. pneumoniae* CPN100630 gene.

Figures 27 through 39 show an identification of T and B cell epitopes from the amino acid sequences shown in the foregoing figures.

DETAILED DESCRIPTION OF INVENTION

Open reading frames (ORFs) encoding chlamydial polypeptides have been identified from the *C. pneumoniae* genome. These polypeptides include polypeptides found permanently in the bacterial membrane structure, polypeptides present in the external vicinity of the bacterial membrane, polypeptides found permanently in the inclusion membrane structure, polypeptides present in the external vicinity of the inclusion membrane, and polypeptides released into the cytoplasm of the infected cell. These polypeptides can be used to prevent and treat *Chlamydia* infection.

According to a first aspect of the invention, isolated polynucleotides are provided which encode the precursor and mature forms of *Chlamydia* polypeptides, whose amino acid sequences are selected from the group consisting of: SEQ ID Nos: 27 to 45.

The term "isolated polynucleotide" is defined as a polynucleotide removed from the environment in which it naturally occurs. For example, a naturally-occurring DNA molecule present in the genome of a living bacteria or as part of a gene bank is not isolated, but the same molecule separated from the remaining part of the bacterial genome, as a result of, *e.g.*, a cloning event (amplification), is isolated. Typically, an isolated DNA molecule is free from DNA regions (*e.g.*, coding regions) with which it is immediately contiguous at the 5' or 3' end, in the naturally occurring genome. Such isolated polynucleotides may be part of a vector or a composition and still be defined as isolated in that such a vector or composition is not part of the natural environment of such polynucleotide.

The polynucleotide of the invention is either RNA or DNA (cDNA, genomic DNA, or synthetic DNA), or modifications, variants, homologs or fragments thereof. The DNA is either double-stranded or single-stranded, and, if single-stranded, is either the coding strand or the non-coding (anti-sense) strand. Any one of the sequences that encode the polypeptides of the invention as shown in SEQ ID Nos: 1 to 26 is (a) a coding sequence, (b) a ribonucleotide sequence derived from transcription of (a), or (c) a coding sequence which uses the redundancy or degeneracy of the genetic code to encode the same polypeptides. By "polypeptide" or "protein" is meant any chain of amino acids, regardless of length or post-translational modification (*e.g.*, glycosylation or phosphorylation). Both terms are used interchangeably in the present application.

Consistent with the first aspect of the invention, amino acid sequences are provided which are homologous to any one of SEQ ID Nos: 27 to 45. As used herein, "homologous amino acid sequence" is any polypeptide which is encoded, in whole or in part, by a nucleic acid sequence which hybridizes at 25-35°C below critical melting temperature (Tm), to any portion of the nucleic acid sequences of SEQ ID Nos: 1 to 26. A homologous amino acid sequence is one that differs from an amino acid sequence shown in any one of SEQ ID Nos: 27 to 45 by one or more amino acid substitutions. Such a sequence also encompass serotypic variants (defined below) as well as sequences containing deletions or insertions which retain inherent characteristics of the polypeptide such as immunogenicity. Preferably, such a sequence is at least 75%, more preferably 80%, and most preferably 90% identical to any one of SEQ ID Nos: 27 to 45. Homologous amino acid sequences include sequences that are identical or substantially identical to SEQ ID Nos: 27 to 45. By "amino acid sequence substantially identical" is meant a sequence that is at least 90%, preferably 95%, more preferably 97%, and most preferably 99% identical to

an amino acid sequence of reference and that preferably differs from the sequence of reference by a majority of conservative amino acid substitutions.

Conservative amino acid substitutions are substitutions among amino acids of the same class. These classes include, for example, amino acids having uncharged polar side chains, such as asparagine, glutamine, serine, threonine, and tyrosine; amino acids having basic side chains, such as lysine, arginine, and histidine; amino acids having acidic side chains, such as aspartic acid and glutamic acid; and amino acids having nonpolar side chains, such as glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, and cysteine.

Homology is measured using sequence analysis software such as Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705. Amino acid sequences are aligned to maximize identity. Gaps may be artificially introduced into the sequence to attain proper alignment. Once the optimal alignment has been set up, the degree of homology is established by recording all of the positions in which the amino acids of both sequences are identical, relative to the total number of positions.

Homologous polynucleotide sequences are defined in a similar way. Preferably, a homologous sequence is one that is at least 45%, more preferably 60%, and most preferably 85% identical to any one of coding sequences SEQ ID Nos: 1 to 26.

Consistent with the first aspect of the invention, polypeptides having a sequence homologous to any one of SEQ ID Nos: 27 to 45 include naturally-occurring allelic variants, as well as mutants or any other non-naturally occurring variants that retain the inherent characteristics of the polypeptide of SEQ ID Nos: 27 to 45.

As is known in the art, an allelic variant is an alternate form of a polypeptide that is characterized as having a substitution, deletion, or addition of one or more amino acids that does not alter the biological function of the polypeptide. By "biological function" is meant the function of the polypeptide in the cells in which it naturally occurs, even if the function is not necessary for the growth or survival of the cells. For example, the biological function of a porin is to allow the entry into cells of compounds present in the extracellular medium. Biological function is distinct from antigenic property. A polypeptide can have more than one biological function.

Allelic variants are very common in nature. For example, a bacterial species such as *C. pneumoniae,* is usually represented by a variety of strains that differ from each other by minor allelic variations. Indeed, a polypeptide that fulfills the same biological function in different strains can have an amino acid sequence (and polynucleotide sequence) that are not identical in each of the strains. Despite this variation, an immune response directed generally against many allelic variants has been demonstrated. In studies of the *Chlamydial* MOMP antigen, cross-strain antibody binding plus neutralization of infectivity occurs despite amino acid sequence variation of MOMP from strain to strain, indicating that the MOMP, when used as an immunogen, is tolerant of amino acid variations.

Polynucleotides encoding homologous polypeptides or allelic variants are retrieved by polymerase chain reaction (PCR) amplification of genomic bacterial DNA extracted by conventional methods. This involves the use of synthetic oligonucleotide primers matching upstream and downstream of the 5' and 3' ends of the encoding domain. Suitable primers are designed according to the nucleotide sequence information provided in SEQ ID Nos:1 to 26. The procedure is as follows: a

primer is selected which consists of 10 to 40, preferably 15 to 25 nucleotides. It is advantageous to select primers containing C and G nucleotides in a proportion sufficient to ensure efficient hybridization; *i.e.*, an amount of C and G nucleotides of at least 40%, preferably 50% of the total nucleotide content.

An alternative method for retrieving polynucleotides encoding homologous polypeptides or allelic variants is by hybridization screening of a DNA or RNA library. Hybridization procedures are well-known in the art and are described in Ausubel *et al.*, (Ref 41), Silhavy *et al.* (Ref 43), and Davis *et al.* (ref 44). Important parameters for optimizing hybridization conditions are reflected in a formula used to obtain the critical melting temperature above which two complementary DNA strands separate from each other (Ref 45). For polynucleotides of about 600 nucleotides or larger, this formula is as follows: Tm = 81.5 + 0.5 x (% G+C) + 1.6 log (positive ion concentration) - 0.6 x (% formamide). Under appropriate stringency conditions, hybridization temperature (Th) is approximately 20 to 40°C, 20 to 25°C, or, preferably 30 to 40°C below the calculated Tm. Those skilled in the art will understand that optimal temperature and salt conditions can be readily determined.

For the polynucleotides of the invention, stringent conditions are achieved for both pre-hybridizing and hybridizing incubations (i) within 4-16 hours at 42°C, in 6 x SSC containing 50% formamide, or (ii) within 4-16 hours at 65°C in an aqueous 6 x SSC solution (1 M NaCl, 0.1 M sodium citrate (pH 7.0)).

Useful homologs and fragments thereof that do not occur naturally are designed using known methods for identifying regions of an antigen that are likely to tolerate amino acid sequence changes and/or deletions. As an example, homologous polypeptides from different species are compared; conserved sequences are identified. The more divergent sequences are the most likely to tolerate sequence changes. Alternatively, sequences are modified such that they become more reactive to T-

and/or B-cells. (See Table below for identification of T- and B- epitopes.) Yet another alternative is to mutate a particular amino acid residue or sequence within the polypeptide *in vitro*, then screen the mutant polypeptides for their ability to prevent or treat Chlamydia infection according to the method outlined below.

A person skilled in the art will readily understand that by following the screening process of this invention, it will be determined without undue experimentation whether a particular homolog of any of SEQ ID Nos: 27 to 45 may be useful in the prevention or treatment of Chlamydia infection. The screening procedure comprises the steps:

(i) immunizing an animal, preferably mouse, with the test homolog or fragment;

(ii) inoculating the immunized animal with Chlamydia; and

(iii) selecting those homologs or fragments which confer protection against Chlamydia.

By "conferring protection" is meant that there is a reduction is severity of any of the effects of Chlamydia infection, in comparison with a control animal which was not immunized with the test homolog or fragment.

It has been previously demonstrated (Yang *et. al.*, 1993) that mice are susceptible to intranasal infection with different isolates of *C. pneumoniae*. Strain AR-39 (Grayston, 1989) was used in Balb/c mice as a challenge infection model to examine the capacity of chlamydia gene products delivered as naked DNA to elicit a protective response against a sublethal *C. pneumoniae* lung infection. Protective immunity is defined as an accelerated clearance of pulmonary infection.

Groups of 7 to 9 week old male Balb/c mice (6 to 10 per group) were immunized intramuscularly (i.m.) plus intranasally (i.n.) with plasmid DNA containing the coding sequence of a *C.pneumoniae* polypeptide. Saline or the plasmid vector lacking

an inserted chlamydial gene was given to groups of control animals.

For i.m. immunization alternate left and right quadriceps were injected with 100µg of DNA in 50µl of PBS on three occasions at 0, 3 and 6 weeks. For i.n. immunization, anaesthetized mice aspirated 50µl of PBS containing 50 µg DNA on three occasions at 0, 3 and 6 weeks. At week 8, immunized mice were inoculated i.n. with 5×10^5 IFU of *C. pneumoniae,* strain AR39 in 100µl of SPG buffer to test their ability to limit the growth of a sublethal *C. pneumoniae* challenge.

Lungs were taken from mice at day 9 post-challenge and immediately homogenised in SPG buffer (7.5% sucrose, 5mM glutamate, 12.5mM phosphate pH7.5). The homogenate was stored frozen at -70°C until assay. Dilutions of the homogenate were assayed for the presence of infectious chlamydia by inoculation onto monolayers of susceptible cells. The inoculum was centrifuged onto the cells at 3000rpm for 1 hour, then the cells were incubated for three days at 35°C in the presence of 1µg/ml cycloheximide. After incubation the monolayers were fixed with formalin and methanol then immunoperoxidase stained for the presence of chlamydial inclusions using convalescent sera from rabbits infected with *C.pneumoniae* and metal-enhanced DAB as a peroxidase substrate.

Consistent with the first aspect of the invention, polypeptide derivatives are provided that are partial sequences of SEQ ID Nos: 27 to 45, partial sequences of polypeptide sequences homologous to SEQ ID Nos: 27 to 45, polypeptides derived from full-length polypeptides by internal deletion, and fusion proteins.

It is an accepted practice in the field of immunology to use fragments and variants of protein immunogens as vaccines, as all that is required to induce an immune response to a protein is a small (*e.g.*, 8 to 10 amino acid) immunogenic region of the

protein. Various short synthetic peptides corresponding to surface-exposed antigens of pathogens other than *Chlamydia* have been shown to be effective vaccine antigens against their respective pathogens, *e.g.* an 11 residue peptide of murine mammary tumor virus (Ref 38), a 16-residue peptide of Semliki Forest virus (Ref 39), and two overlapping peptides of 15 residues each from canine parvovirus (Ref 40).

Accordingly, it will be readily apparent to one skilled in the art, having read the present description, that partial sequences of SEQ ID Nos: 27 to 45 or their homologous amino acid sequences are inherent to the full-length sequences and are taught by the present invention. Such polypeptide fragments preferably are at least 12 amino acids in length. Advantageously, they are at least 20 amino acids, preferably at least 50 amino acids, more preferably at least 75 amino acids, and most preferably at least 100 amino acids in length.

Polynucleotides of 30 to 600 nucleotides encoding partial sequences of sequences homologous to SEQ ID Nos: 27 to 45 are retrieved by PCR amplification using the parameters outlined above and using primers matching the sequences upstream and downstream of the 5' and 3' ends of the fragment to be amplified. The template polynucleotide for such amplification is either the full length polynucleotide homologous to one of SEQ ID Nos: 1 to 26, or a polynucleotide contained in a mixture of polynucleotides such as a DNA or RNA library. As an alternative method for retrieving the partial sequences, screening hybridization is carried out under conditions described above and using the formula for calculating Tm. Where fragments of 30 to 600 nucleotides are to be retrieved, the calculated Tm is corrected by subtracting (600/polynucleotide size in base pairs) and the stringency conditions are defined by a hybridization temperature that is 5 to 10°C below Tm. Where oligonucleotides shorter than 20-30 bases are to be obtained, the formula for calculating the Tm is as follows: Tm = 4 x (G+C)

+ 2 (A+T). For example, an 18 nucleotide fragment of 50% G+C would have an approximate Tm of 54°C. Short peptides that are fragments of SEQ. ID Nos. 27 to 45 or their homologous sequences, are obtained directly by chemical synthesis (E. Gross and H. J. Meinhofer, 4 The Peptides: Analysis, Synthesis, Biology; Modern Techniques of Peptide Synthesis, John Wiley & Sons (1981), and M. Bodanzki, Principles of Peptide Synthesis, Springer -Verlag (1984)).

Useful polypeptide derivatives, *e.g.*, polypeptide fragments, are designed using computer-assisted analysis of amino acid sequences. This identifies probable surface-exposed, antigenic regions (Ref 37). An analysis of the 13 amino acid sequences contained in SEQ ID Nos: 27 to 45, based on the product of flexibility and hydrophobicity propensities using the program SEQSEE (Wishart DS, et al. "SEQSEE: a comprehensive program suite for protein sequence analysis." *Comput Appl Biosci*. 1994 Apr;10(2):121-32), reveal a number of potential B- and T-cell epitopes which may be used as a basis for selecting useful immunogenic fragments and variants. The results are shown in Figures 27 to 39. This analysis uses a reasonable combination of external surface features that is likely to be recognized by antibodies. Probable T-cell epitopes for HLA-A0201 MHC subclass were revealed by an algorithm written at Connaught Laboratories that emulates an approach developed at the NIH (Parker KC, *et al.* "Peptide binding to MHC class I molecules: implications for antigenic peptide prediction." *Immunol Res* 1995;14(1):34-57).

Epitopes which induce a protective T cell-dependent immune response are present throughout the length of the polypeptide. However, some epitopes may be masked by secondary and tertiary structures of the polypeptide. To reveal such masked epitopes large internal deletions are created which remove much of the original protein structure and exposes the masked epitopes. Such internal deletions sometimes effects the

additional advantage of removing immunodominant regions of high variability among strains. Polynucleotides encoding polypeptide fragments and polypeptides having large internal deletions are constructed using standard methods (Ref 41). Such methods include standard PCR, inverse PCR, restriction enzyme treatment of cloned DNA molecules, or the method of Kunkel *et al.* (Ref 42). Components for these methods and instructions for their use are readily available from various commercial sources such as Stratagene. Once the deletion mutants have been constructed, they are tested for their ability to prevent or treat Chlamydia infection as described above.

As used herein, a fusion polypeptide is one that contains a polypeptide or a polypeptide derivative of the invention fused at the N- or C-terminal end to any other polypeptide (hereinafter referred to as a peptide tail). A simple way to obtain such a fusion polypeptide is by translation of an in-frame fusion of the polynucleotide sequences, *i.e.*, a hybrid gene. The hybrid gene encoding the fusion polypeptide is inserted into an expression vector which is used to transform or transfect a host cell. Alternatively, the polynucleotide sequence encoding the polypeptide or polypeptide derivative is inserted into an expression vector in which the polynucleotide encoding the peptide tail is already present. Such vectors and instructions for their use are commercially available, *e.g.* the pMal-c2 or pMal-p2 system from New England Biolabs, in which the peptide tail is a maltose binding protein, the glutathione-S-transferase system of Pharmacia, or the His-Tag system available from Novagen. These and other expression systems provide convenient means for further purification of polypeptides and derivatives of the invention.

An advantageous example of a fusion polypeptide is one where the polypeptide or homolog or fragment of the invention is fused to a polypeptide having adjuvant activity, such as subunit B of either cholera toxin or *E. coli* heat-labile toxin. Another

advantageous fusion is one where the polypeptide, homolog or fragment is fused to a strong T-cell epitope or B-cell epitope. Such an epitope may be one known in the art (*e.g.* the Hepatitis B virus core antigen, D.R. Millich et al., "Antibody production to the nucleocapsid and envelope of the Hepatitis B virus primed by a single synthetic T cell site", Nature. 1987. 329:547-549), or one which has been identified in another polypeptide of the invention (Table). Consistent with this aspect of the invention is a fusion polypeptide comprising T- or B-cell epitopes from one of SEQ ID Nos: 27 to 45 or its homolog or fragment, wherein the epitopes are derived from multiple variants of said polypeptide or homolog or fragment, each variant differing from another in the location and sequence of its epitope within the polypeptide. Such a fusion is effective in the prevention and treatment of Chlamydia infection since it optimizes the T- and B-cell response to the overall polypeptide, homolog or fragment.

To effect fusion, the polypeptide of the invention is fused to the N-, or preferably, to the C-terminal end of the polypeptide having adjuvant activity or T- or B-cell epitope. Alternatively, a polypeptide fragment of the invention is inserted internally within the amino acid sequence of the polypeptide having adjuvant activity. The T- or B-cell epitope may also be inserted internally within the amino acid sequence of the polypeptide of the invention.

Consistent with the first aspect, the polynucleotides of the invention also encode hybrid precursor polypeptides containing heterologous signal peptides, which mature into polypeptides of the invention. By "heterologous signal peptide" is meant a signal peptide that is not found in naturally-occurring precursors of polypeptides of the invention.

A polynucleotide molecule according to the invention, including RNA, DNA, or modifications or combinations thereof, have various applications. A DNA molecule is used, for example,

(i) in a process for producing the encoded polypeptide in a recombinant host system, (ii) in the construction of vaccine vectors such as poxviruses, which are further used in methods and compositions for preventing and/or treating *Chlamydia* infection, (iii) as a vaccine agent (as well as an RNA molecule), in a naked form or formulated with a delivery vehicle and, (iv) in the construction of attenuated *Chlamydia* strains that can over-express a polynucleotide of the invention or express it in a non-toxic, mutated form.

Accordingly, a second aspect of the invention encompasses (i) an expression cassette containing a DNA molecule of the invention placed under the control of the elements required for expression, in particular under the control of an appropriate promoter; (ii) an expression vector containing an expression cassette of the invention; (iii) a procaryotic or eucaryotic cell transformed or transfected with an expression cassette and/or vector of the invention, as well as (iv) a process for producing a polypeptide or polypeptide derivative encoded by a polynucleotide of the invention, which involves culturing a procaryotic or eucaryotic cell transformed or transfected with an expression cassette and/or vector of the invention, under conditions that allow expression of the DNA molecule of the invention and, recovering the encoded polypeptide or polypeptide derivative from the cell culture.

A recombinant expression system is selected from procaryotic and eucaryotic hosts. Eucaryotic hosts include yeast cells (*e.g.*, *Saccharomyces cerevisiae* or *Pichia pastoris*), mammalian cells (*e.g.*, COS1, NIH3T3, or JEG3 cells), arthropods cells (*e.g.*, *Spodoptera frugiperda* (SF9) cells), and plant cells. A preferred expression system is a procaryotic host such as *E. coli*. Bacterial and eucaryotic cells are available from a number of different sources including commercial sources to those skilled in the art, *e.g.*, the American Type Culture Collection (ATCC; Rockville, Maryland). Commercial sources of

cells used for recombinant protein expression also provide instructions for usage of the cells.

The choice of the expression system depends on the features desired for the expressed polypeptide. For example, it may be useful to produce a polypeptide of the invention in a particular lipidated form or any other form.

One skilled in the art would redily understand that not all vectors and expression control sequences and hosts would be expected to express equally well the polynucleotides of this invention. With the guidelines described below, however, a selection of vectors, expression control sequences and hosts may be made without undue experimentation and without departing from the scope of this invention.

In selecting a vector, the host must be chosen that is compatible with the vector which is to exist and possibly replicate in it. Considerations are made with respect to the vector copy number, the ability to control the copy number, expression of other proteins such as antibiotic resistance. In selecting an expression control sequence, a number of variables are considered. Among the important variable are the relative strength of the sequence (*e.g.* the ability to drive expression under various conditions), the ability to control the sequence's function, compatibility between the polynucleotide to be expressed and the control sequence (*e.g.* secondary structures are considered to avoid hairpin structures which prevent efficient transcription). In selecting the host, unicellular hosts are selected which are compatible with the selected vector, tolerant of any possible toxic effects of the expressed product, able to secrete the expressed product efficiently if such is desired, to be able to express the product in the desired conformation, to be easily scaled up, and to which ease of purification of the final product.

The choice of the expression cassette depends on the host system selected as well as the features desired for the

expressed polypeptide. Typically, an expression cassette includes a promoter that is functional in the selected host system and can be constitutive or inducible; a ribosome binding site; a start codon (ATG) if necessary; a region encoding a signal peptide, *e.g.*, a lipidation signal peptide; a DNA molecule of the invention; a stop codon; and optionally a 3' terminal region (translation and/or transcription terminator). The signal peptide encoding region is adjacent to the polynucleotide of the invention and placed in proper reading frame. The signal peptide-encoding region is homologous or heterologous to the DNA molecule encoding the mature polypeptide and is compatible with the secretion apparatus of the host used for expression. The open reading frame constituted by the DNA molecule of the invention, solely or together with the signal peptide, is placed under the control of the promoter so that transcription and translation occur in the host system. Promoters and signal peptide encoding regions are widely known and available to those skilled in the art and include, for example, the promoter of *Salmonella typhimurium* (and derivatives) that is inducible by arabinose (promoter araB) and is functional in Gram-negative bacteria such as *E. coli* (as described in U.S. Patent No. 5,028,530 and in Cagnon *et al.*, (Ref 46)); the promoter of the gene of bacteriophage T7 encoding RNA polymerase, that is functional in a number of *E. coli* strains expressing T7 polymerase (described in U.S. Patent No. 4,952,496); OspA lipidation signal peptide ; and RlpB lipidation signal peptide (Ref 47).

The expression cassette is typically part of an expression vector, which is selected for its ability to replicate in the chosen expression system. Expression vectors (*e.g.*, plasmids or viral vectors) can be chosen, for example, from those described in Pouwels *et al.* (Cloning Vectors: A Laboratory Manual 1985, Supp. 1987). Suitable expression vectors can be purchased from various commercial sources.

Methods for transforming/transfecting host cells with expression vectors are well-known in the art and depend on the host system selected as described in Ausubel *et al.*, (Ref 41).

Upon expression, a recombinant polypeptide of the invention (or a polypeptide derivative) is produced and remains in the intracellular compartment, is secreted/excreted in the extracellular medium or in the periplasmic space, or is embedded in the cellular membrane. The polypeptide is recovered in a substantially purified form from the cell extract or from the supernatant after centrifugation of the recombinant cell culture. Typically, the recombinant polypeptide is purified by antibody-based affinity purification or by other well-known methods that can be readily adapted by a person skilled in the art, such as fusion of the polynucleotide encoding the polypeptide or its derivative to a small affinity binding domain. Antibodies useful for purifying by immunoaffinity the polypeptides of the invention are obtained as described below.

A polynucleotide of the invention can also be useful as a vaccine. There are two major routes, either using a viral or bacterial host as gene delivery vehicle (live vaccine vector) or administering the gene in a free form, *e.g.*, inserted into a plasmid. Therapeutic or prophylactic efficacy of a polynucleotide of the invention is evaluated as described below.

Accordingly, a third aspect of the invention provides (i) a vaccine vector such as a poxvirus, containing a DNA molecule of the invention, placed under the control of elements required for expression; (ii) a composition of matter comprising a vaccine vector of the invention, together with a diluent or carrier; specifically (iii) a pharmaceutical composition containing a therapeutically or prophylactically effective amount of a vaccine vector of the invention; (iv) a method for inducing an immune response against *Chlamydia* in a mammal (*e.g.*, a human; alternatively, the method can be used in veterinary applications for treating or preventing *Chlamydia* infection of

animals, *e.g.*, cats or birds), which involves administering to the mammal an immunogenically effective amount of a vaccine vector of the invention to elicit a protective or therapeutic immune response to *Chlamydia* ; and particularly, (v) a method for preventing and/or treating a *Chlamydia* (*e.g.*, *C. trachomatis, C. psittaci, C. pneumonia, C. pecorum*) infection, which involves administering a prophylactic or therapeutic amount of a vaccine vector of the invention to an infected individual. Additionally, the third aspect of the invention encompasses the use of a vaccine vector of the invention in the preparation of a medicament for preventing and/or treating *Chlamydia* infection.

As used herein, a vaccine vector expresses one or several polypeptides or derivatives of the invention, as well as at least one additional *Chlamydia* antigen (??), fragment, homolog, mutant, or derivative thereof. The vaccine vector may express additionally a cytokine, such as interleukin-2 (IL-2) or interleukin-12 (IL-12), that enhances the immune response (adjuvant effect). It is understood that each of the components to be expressed is placed under the control of elements required for expression in a mammalian cell.

Consistent with the third aspect of the invention is a composition comprising several vaccine vectors, each of them capable of expressing a polypeptide or derivative of the invention. A composition may also comprise a vaccine vector capable of expressing an additional *Chlamydia* antigen, or a subunit, fragment, homolog, mutant, or derivative thereof; or a cytokine such as IL-2 or IL-12.

Vaccination methods for treating or preventing infection in a mammal comprises use of a vaccine vector of the invention to be administered by any conventional route , particularly to a mucosal (*e.g.*, ocular, intranasal, oral, gastric, pulmonary, intestinal, rectal, vaginal, or urinary tract) surface or *via* the parenteral (*e.g.*, subcutaneous, intradermal, intramuscular,

intravenous, or intraperitoneal) route. Preferred routes depend upon the choice of the vaccine vector. Treatment may be effected in a single dose or repeated at intervals. The appropriate dosage depends on various parameters understood by skilled artisans such as the vaccine vector itself, the route of administration or the condition of the mammal to be vaccinated (weight, age and the like).

Live vaccine vectors available in the art include viral vectors such as adenoviruses and poxviruses as well as bacterial vectors, *e.g.*, *Shigella*, *Salmonella*, *Vibrio cholerae*, *Lactobacillus*, Bacille bilié de Calmette-Guérin (BCG), and *Streptococcus*.

An example of an adenovirus vector, as well as a method for constructing an adenovirus vector capable of expressing a DNA molecule of the invention, are described in U.S. Patent No. 4,920,209. Poxvirus vectors include vaccinia and canary pox virus, described in U.S. Patent No. 4,722,848 and U.S. Patent No. 5,364,773, respectively. (Also see, *e.g.*, Tartaglia *et al.*, Virology (1992) 188:217) for a description of a vaccinia virus vector and Taylor *et al*, Vaccine (1995) 13:539 for a reference of a canary pox.) Poxvirus vectors capable of expressing a polynucleotide of the invention are obtained by homologous recombination as described in Kieny *et al.*, Nature (1984) 312:163 so that the polynucleotide of the invention is inserted in the viral genome under appropriate conditions for expression in mammalian cells. Generally, the dose of vaccine viral vector, for therapeutic or prophylactic use, can be of from about $1x10^4$ to about $1x10^{11}$, advantageously from about $1x10^7$ to about $1x10^{10}$, preferably of from about $1x10^7$ to about $1x10^9$ plaque-forming units per kilogram. Preferably, viral vectors are administered parenterally; for example, in 3 doses, 4 weeks apart. It is preferable to avoid adding a chemical adjuvant to a composition containing a viral vector of the invention and

thereby minimizing the immune response to the viral vector itself.

Non-toxicogenic *Vibrio cholerae* mutant strains that are useful as a live oral vaccine are known. Mekalanos *et al.*, Nature (1983) 306:551 and U.S. Patent No. 4,882,278 describe strains which have a substantial amount of the coding sequence of each of the two *ctxA* alleles deleted so that no functional *cholerae* toxin is produced. WO 92/11354 describes a strain in which the *irgA* locus is inactivated by mutation; this mutation can be combined in a single strain with *ctxA* mutations. WO 94/1533 describes a deletion mutant lacking functional *ctxA* and *attRS1* DNA sequences. These mutant strains are genetically engineered to express heterologous antigens, as described in WO 94/19482. An effective vaccine dose of a *Vibrio cholerae* strain capable of expressing a polypeptide or polypeptide derivative encoded by a DNA molecule of the invention contains about $1x10^5$ to about $1x10^9$, preferably about $1x10^6$ to about $1x10^8$, viable bacteria in a volume appropriate for the selected route of administration. Preferred routes of administration include all mucosal routes; most preferably, these vectors are administered intranasally or orally.

Attenuated *Salmonella typhimurium* strains, genetically engineered for recombinant expression of heterologous antigens or not, and their use as oral vaccines are described in Nakayama *et al.* (Bio/Technology (1988) 6:693) and WO 92/11361. Preferred routes of administration include all mucosal routes; most preferably, these vectors are administered intranasally or orally.

Other bacterial strains used as vaccine vectors in the context of the present invention are described in High *et al.*, EMBO (1992) 11:1991 and Sizemore *et al.*, Science (1995) 270:299 (*Shigella flexneri*); Medaglini *et al.*, Proc. Natl. Acad. Sci. USA (1995) 92:6868 (*Streptococcus gordonii*) , Flynn J.L., Cell.

Mol. Biol. (1994) 40 (suppl. I):31, WO 88/6626, WO 90/0594, WO 91/13157, WO 92/1796, and WO 92/21376 (Bacille Calmette Guerin).

In bacterial vectors, the polynucleotide of the invention is inserted into the bacterial genome or remains in a free state as part of a plasmid.

The composition comprising a vaccine bacterial vector of the present invention may further contain an adjuvant . A number of adjuvants are known to those skilled in the art. Preferred adjuvants are selected from the list provided below.

Accordingly, a fourth aspect of the invention provides (i) a composition of matter comprising a polynucleotide of the invention, together with a diluent or carrier; (ii) a pharmaceutical composition comprising a therapeutically or prophylactically effective amount of a polynucleotide of the invention; (iii) a method for inducing an immune response against *Chlamydia* in a mammal by administration of an immunogenically effective amount of a polynucleotide of the invention to elicit a protective immune response to *Chlamydia;* and particularly, (iv) a method for preventing and/or treating a *Chlamydia* (*e.g., C. trachomatis, C. psittaci, C. pneumoniae, or C. pecorum*) infection, by administering a prophylactic or therapeutic amount of a polynucleotide of the invention to an infected individual. Additionally, the fourth aspect of the invention encompasses the use of a polynucleotide of the invention in the preparation of a medicament for preventing and/or treating *Chlamydia* infection. A preferred use includes the use of a DNA molecule placed under conditions for expression in a mammalian cell, especially in a plasmid that is unable to replicate in mammalian cells and to substantially integrate in a mammalian genome.

Use of the polynucleotides of the invention include their administration to a mammal as a vaccine, for therapeutic or prophylactic purposes. Such polynucleotides are used in the form of DNA as part of a plasmid that is unable to replicate in

a mammalian cell and unable to integrate into the mammalian genome. Typically, such a DNA molecule is placed under the control of a promoter suitable for expression in a mammalian cell. The promoter functions either ubiquitously or tissue-specifically. Examples of non-tissue specific promoters include the early Cytomegalovirus (CMV) promoter (described in U.S. Patent No. 4,168,062) and the Rous Sarcoma Virus promoter (described in Norton & Coffin, Molec. Cell Biol. (1985) 5:281). An example of a tissue-specific promoter is the desmin promoter which drives expression in muscle cells (Li *et al.*, Gene (1989) 78:243, Li & Paulin, J. Biol. Chem. (1991) 266:6562 and Li & Paulin, J. Biol. Chem. (1993) 268:10403). Use of promoters is well-known to those skilled in the art. Useful vectors are described in numerous publications, specifically WO 94/21797 and Hartikka *et al.*, Human Gene Therapy (1996) 7:1205.

Polynucleotides of the invention which are used as a vaccine encode either a precursor or a mature form of the corresponding polypeptide. In the precursor form, the signal peptide is either homologous or heterologous. In the latter case, a eucaryotic leader sequence such as the leader sequence of the tissue-type plasminogen factor (tPA) is preferred.

As used herein, a composition of the invention contains one or several polynucleotides with optionally at least one additional polynucleotide encoding another *Chlamydia* antigen such as urease subunit A, B, or both, or a fragment, derivative, mutant, or analog thereof. The composition may also contain an additional polynucleotide encoding a cytokine, such as interleukin-2 (IL-2) or interleukin-12 (IL-12) so that the immune response is enhanced. These additional polynucleotides are placed under appropriate control for expression. Advantageously, DNA molecules of the invention and/or additional DNA molecules to be included in the same composition, are present in the same plasmid.

Standard techniques of molecular biology for preparing and purifying polynucleotides are used in the preparation of polynucleotide therapeutics of the invention. For use as a vaccine, a polynucleotide of the invention is formulated according to various methods outlined below.

One method utililizes the polynucleotide in a naked form, free of any delivery vehicles. Such a polynucleotide is simply diluted in a physiologically acceptable solution such as sterile saline or sterile buffered saline, with or without a carrier. When present, the carrier preferably is isotonic, hypotonic, or weakly hypertonic, and has a relatively low ionic strength, such as provided by a sucrose solution, *e.g.*, a solution containing 20% sucrose.

An alternative method utilizes the polynucleotide in association with agents that assist in cellular uptake. Examples of such agents are (i) chemicals that modify cellular permeability, such as bupivacaine (see, *e.g.*, WO 94/16737), (ii) liposomes for encapsulation of the polynucleotide, or (iii) cationic lipids or silica, gold, or tungsten microparticles which associate themselves with the polynucleotides.

Anionic and neutral liposomes are well-known in the art (see, *e.g.*, Liposomes: A Practical Approach, RPC New Ed, IRL press (1990), for a detailed description of methods for making liposomes) and are useful for delivering a large range of products, including polynucleotides. Cationic lipids are also known in the art and are commonly used for gene delivery. Such lipids include Lipofectin™ also known as DOTMA (N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride), DOTAP (1,2-bis(oleyloxy)-3-(trimethylammonio)propane), DDAB (dimethyldioctadecylammonium bromide), DOGS (dioctadecylamidologlycyl spermine) and cholesterol derivatives such as DC-Chol (3 beta-(N-(N',N'-dimethyl aminomethane)-carbamoyl) cholesterol). A description of these cationic lipids

can be found in EP 187,702, WO 90/11092, U.S. Patent No. 5,283,185, WO 91/15501, WO 95/26356, and U.S. Patent No. 5,527,928. Cationic lipids for gene delivery are preferably used in association with a neutral lipid such as DOPE (dioleyl phosphatidylethanolamine), as described in WO 90/11092 as an example.

Formulation containing cationic liposomes may optionally contain other transfection-facilitating compounds. A number of them are described in WO 93/18759, WO 93/19768, WO 94/25608, and WO 95/2397. They include spermine derivatives useful for facilitating the transport of DNA through the nuclear membrane (see, for example, WO 93/18759) and membrane-permeabilizing compounds such as GALA, Gramicidine S, and cationic bile salts (see, for example, WO 93/19768).

Gold or tungsten microparticles are used for gene delivery, as described in WO 91/359, WO 93/17706, and Tang *et al.* (Nature (1992) 356:152). The microparticle-coated polynucleotide is injected *via* intradermal or intraepidermal routes using a needleless injection device ("gene gun"), such as those described in U.S. Patent No. 4,945,050, U.S. Patent No. 5,015,580, and WO 94/24263.

The amount of DNA to be used in a vaccine recipient depends, *e.g.*, on the strength of the promoter used in the DNA construct, the immunogenicity of the expressed gene product, the condition of the mammal intended for administration (*e.g.*, the weight, age, and general health of the mammal), the mode of administration, and the type of formulation. In general, a therapeutically or prophylactically effective dose from about 1 µg to about 1 mg, preferably, from about 10 µg to about 800 µg and, more preferably, from about 25 µg to about 250 µg, can be administered to human adults. The administration can be achieved in a single dose or repeated at intervals.

The route of administration is any conventional route used in the vaccine field. As general guidance, a

polynucleotide of the invention is administered *via* a mucosal surface, *e.g.*, an ocular, intranasal, pulmonary, oral, intestinal, rectal, vaginal, and urinary tract surface; or *via* a parenteral route, *e.g.*, by an intravenous, subcutaneous, intraperitoneal, intradermal, intraepidermal, or intramuscular route. The choice of administration route depends on the formulation that is selected. A polynucleotide formulated in association with bupivacaine is advantageously administered into muscles. When a neutral or anionic liposome or a cationic lipid, such as DOTMA or DC-Chol, is used, the formulation can be advantageously injected *via* intravenous, intranasal (aerosolization), intramuscular, intradermal, and subcutaneous routes. A polynucleotide in a naked form can advantageously be administered *via* the intramuscular, intradermal, or sub-cutaneous routes.

Although not absolutely required, such a composition can also contain an adjuvant. If so, a systemic adjuvant that does not require concomitant administration in order to exhibit an adjuvant effect is preferable such as, *e.g.*, QS21, which is described in U.S. Patent No. 5,057,546.

The sequence information provided in the present application enables the design of specific nucleotide probes and primers that are used for diagnostic purposes. Accordingly, a fifth aspect of the invention provides a nucleotide probe or primer having a sequence found in or derived by degeneracy of the genetic code from a sequence shown in any one of SEQ ID Nos:1 to 26.

The term "probe" as used in the present application refers to DNA (preferably single stranded) or RNA molecules (or modifications or combinations thereof) that hybridize under the stringent conditions, as defined above, to nucleic acid molecules having SEQ ID Nos: 1 to 26 or to sequences homologous to SEQ ID Nos:1 to 26, or to their complementary or anti-sense sequences. Generally, probes are significantly shorter than

full-length sequences . Such probes contain from about 5 to about 100, preferably from about 10 to about 80, nucleotides. In particular, probes have sequences that are at least 75%, preferably at least 85%, more preferably 95% homologous to a portion of any of SEQ ID Nos:1 to 26 or that are complementary to such sequences. Probes may contain modified bases such as inosine, methyl-5-deoxycytidine, deoxyuridine, dimethylamino-5-deoxyuridine, or diamino-2, 6-purine. Sugar or phosphate residues may also be modified or substituted. For example, a deoxyribose residue may be replaced by a polyamide (Nielsen *et al.*, Science (1991) 254:1497) and phosphate residues may be replaced by ester groups such as diphosphate, alkyl, arylphosphonate and phosphorothioate esters. In addition, the 2'-hydroxyl group on ribonucleotides may be modified by including such groups as alkyl groups.

Probes of the invention are used in diagnostic tests, as capture or detection probes. Such capture probes are conventionally immobilized on a solid support, directly or indirectly, by covalent means or by passive adsorption. A detection probe is labelled by a detection marker selected from: radioactive isotopes, enzymes such as peroxidase, alkaline phosphatase, and enzymes able to hydrolyze a chromogenic, fluorogenic, or luminescent substrate, compounds that are chromogenic, fluorogenic, or luminescent, nucleotide base analogs, and biotin.

Probes of the invention are used in any conventional hybridization technique, such as dot blot (Maniatis *et al.*, Molecular Cloning: A Laboratory Manual (1982) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), Southern blot (Southern, J. Mol. Biol. (1975) 98:503), northern blot (identical to Southern blot with the exception that RNA is used as a target), or the sandwich technique (Dunn *et al.*, Cell (1977) 12:23). The latter technique involves the use of a specific capture probe and/or a specific detection probe with

nucleotide sequences that at least partially differ from each other.

A primer is a probe of usually about 10 to about 40 nucleotides that is used to initiate enzymatic polymerization of DNA in an amplification process (*e.g.*, PCR), in an elongation process, or in a reverse transcription method. Primers used in diagnostic methods involving PCR are labeled by methods known in the art.

As described herein, the invention also encompasses (i) a reagent comprising a probe of the invention for detecting and/or identifying the presence of *Chlamydia* in a biological material; (ii) a method for detecting and/or identifying the presence of *Chlamydia* in a biological material, in which (a) a sample is recovered or derived from the biological material, (b) DNA or RNA is extracted from the material and denatured, and (c) exposed to a probe of the invention, for example, a capture, detection probe or both, under stringent hybridization conditions, such that hybridization is detected; and (iii) a method for detecting and/or identifying the presence of *Chlamydia* in a biological material, in which (a) a sample is recovered or derived from the biological material, (b) DNA is extracted therefrom, (c) the extracted DNA is primed with at least one, and preferably two, primers of the invention and amplified by polymerase chain reaction, and (d) the amplified DNA fragment is produced.

It is apparent that disclosure of polynucleotide sequences of SEQ ID Nos: 1 to 26, their homolog, and partial sequences of either enable their corresponding amino acid sequences. Accordingly, a sixth aspect of the invention features a substantially purified polypeptide or polypeptide derivative having an amino acid sequence encoded by a polynucleotide of the invention.

A "substantially purified polypeptide" as used herein is defined as a polypeptide that is separated from the environment

in which it naturally occurs and/or that is free of the majority of the polypeptides that are present in the environment in which it was synthesized. For example, a substantially purified polypeptide is free from cytoplasmic polypeptides. Those skilled in the art would readily understand that the polypeptides of the invention may be purified from a natural source, *i.e.*, a *Chlamydia* strain, or produced by recombinant means.

Consistent with the sixth aspect of the invention are polypeptides, homologs or fragments which are modified or treated to enhance their immunogenicity in the target animal, in whom the polypeptide, homolog or fragments are intended to confer protection against Chlamydia. Such modifications or treatments include: amino acid substitutions with an amino acid derivative such as 3-methyhistidine, 4-hydroxyproline, 5-hydroxylysine etc., modifications or deletions which are carried out after preparation of the polypeptide, homolog or fragment, such as the modification of free amino, carboxyl or hydroxyl side groups of the amino acids.

Identification of homologous polypeptides or polypeptide derivatives encoded by polynucleotides of the invention which have specific antigenicity is achieved by screening for cross-reactivity with an antiserum raised against the polypeptide of reference having an amino acid sequence of any one of SEQ ID Nos: 27 to 45. The procedure is as follows: a monospecific hyperimmune antiserum is raised against a purified reference polypeptide, a fusion polypeptide (for example, an expression product of MBP, GST, or His-tag systems), or a synthetic peptide predicted to be antigenic. Where an antiserum is raised against a fusion polypeptide, two different fusion systems are employed. Specific antigenicity can be determined according to a number of methods, including Western blot (Towbin *et al.*, Proc. Natl. Acad. Sci. USA (1979) 76:4350), dot blot, and ELISA, as described below.

In a Western blot assay, the product to be screened, either as a purified preparation or a total *E. coli* extract, is submitted to SDS-Page electrophoresis as described by Laemmli (Nature (1970) 227:680). After transfer to a nitrocellulose membrane, the material is further incubated with the monospecific hyperimmune antiserum diluted in the range of dilutions from about 1:5 to about 1:5000, preferably from about 1:100 to about 1:500. Specific antigenicity is shown once a band corresponding to the product exhibits reactivity at any of the dilutions in the above range.

In an ELISA assay, the product to be screened is preferably used as the coating antigen. A purified preparation is preferred, although a whole cell extract can also be used. Briefly, about 100 µl of a preparation at about 10 µg protein/ml are distributed into wells of a 96-well polycarbonate ELISA plate. The plate is incubated for 2 hours at 37°C then overnight at 4°C. The plate is washed with phosphate buffer saline (PBS) containing 0.05% Tween 20 (PBS/Tween buffer). The wells are saturated with 250 µl PBS containing 1% bovine serum albumin (BSA) to prevent non-specific antibody binding. After 1 hour incubation at 37°C, the plate is washed with PBS/Tween buffer. The antiserum is serially diluted in PBS/Tween buffer containing 0.5% BSA. 100 µl of dilutions are added per well. The plate is incubated for 90 minutes at 37°C, washed and evaluated according to standard procedures. For example, a goat anti-rabbit peroxidase conjugate is added to the wells when specific antibodies were raised in rabbits. Incubation is carried out for 90 minutes at 37°C and the plate is washed. The reaction is developed with the appropriate substrate and the reaction is measured by colorimetry (absorbance measured spectrophotometrically). Under the above experimental conditions, a positive reaction is shown by O.D. values greater than a non immune control serum.

In a dot blot assay, a purified product is preferred, although a whole cell extract can also be used. Briefly, a solution of the product at about 100 µg/ml is serially two-fold diluted in 50 mM Tris-HCl (pH 7.5). 100 µl of each dilution are applied to a nitrocellulose membrane 0.45 µm set in a 96-well dot blot apparatus (Biorad). The buffer is removed by applying vacuum to the system. Wells are washed by addition of 50 mM Tris-HCl (pH 7.5) and the membrane is air-dried. The membrane is saturated in blocking buffer (50 mM Tris-HCl (pH 7.5) 0.15 M NaCl, 10 g/L skim milk) and incubated with an antiserum dilution from about 1:50 to about 1:5000, preferably about 1:500. The reaction is revealed according to standard procedures. For example, a goat anti-rabbit peroxidase conjugate is added to the wells when rabbit antibodies are used. Incubation is carried out 90 minutes at 37°C and the blot is washed. The reaction is developed with the appropriate substrate and stopped. The reaction is measured visually by the appearance of a colored spot, *e.g.*, by colorimetry. Under the above experimental conditions, a positive reaction is shown once a colored spot is associated with a dilution of at least about 1:5, preferably of at least about 1:500.

Therapeutic or prophylactic efficacy of a polypeptide or derivative of the invention can be evaluated as described below. A seventh aspect of the invention provides (i) a composition of matter comprising a polypeptide of the invention together with a diluent or carrier; specifically (ii) a pharmaceutical composition containing a therapeutically or prophylactically effective amount of a polypeptide of the invention; (iii) a method for inducing an immune response against *Chlamydia* in a mammal, by administering to the mammal an immunogenically effective amount of a polypeptide of the invention to elicit a protective immune response to *Chlamydia*; and particularly, (iv) a method for preventing and/or treating a *Chlamydia* (*e.g.*, *C. trachomatis. C. psittaci, C. pneumoniae.* or *C. pecorum*)

infection, by administering a prophylactic or therapeutic amount of a polypeptide of the invention to an infected individual. Additionally, the seventh aspect of the invention encompasses the use of a polypeptide of the invention in the preparation of a medicament for preventing and/or treating *Chlamydia* infection.

As used herein, the immunogenic compositions of the invention are administered by conventional routes known the vaccine field, in particular to a mucosal (*e.g.*, ocular, intranasal, pulmonary, oral, gastric, intestinal, rectal, vaginal, or urinary tract) surface or *via* the parenteral (*e.g.*, subcutaneous, intradermal, intramuscular, intravenous, or intraperitoneal) route. The choice of administration route depends upon a number of parameters, such as the adjuvant associated with the polypeptide. If a mucosal adjuvant is used, the intranasal or oral route is preferred. If a lipid formulation or an aluminum compound is used, the parenteral route is preferred with the sub-cutaneous or intramuscular route being most preferred. The choice also depends upon the nature of the vaccine agent. For example, a polypeptide of the invention fused to CTB or LTB is best administered to a mucosal surface.

As used herein, the composition of the invention contains one or several polypeptides or derivatives of the invention. The composition optionally contains at least one additional *Chlamydia* antigen, or a subunit, fragment, homolog, mutant, or derivative thereof.

For use in a composition of the invention, a polypeptide or derivative thereof is formulated into or with liposomes, preferably neutral or anionic liposomes, microspheres, ISCOMS, or virus-like-particles (VLPs) to facilitate delivery and/or enhance the immune response. These compounds are readily available to one skilled in the art; for example, see Liposomes: A Practical Approach (*supra*).

Adjuvants other than liposomes and the like are also used and are known in the art. Adjuvants may protect the antigen from rapid dispersal by sequestering it in a local deposit, or they may contain substances that stimulate the host to secrete factors that are chemotactic for macrophages and other components of the immune system. An appropriate selection can conventionally be made by those skilled in the art, for example, from those described below.

Treatment is achieved in a single dose or repeated as necessary at intervals, as can be determined readily by one skilled in the art. For example, a priming dose is followed by three booster doses at weekly or monthly intervals. An appropriate dose depends on various parameters including the recipient (*e.g.*, adult or infant), the particular vaccine antigen, the route and frequency of administration, the presence/absence or type of adjuvant, and the desired effect (*e.g.*, protection and/or treatment), as can be determined by one skilled in the art. In general, a vaccine antigen of the invention is administered by a mucosal route in an amount from about 10 µg to about 500 mg, preferably from about 1 mg to about 200 mg. For the parenteral route of administration, the dose usually does not exceed about 1 mg, preferably about 100 µg.

When used as vaccine agents, polynucleotides and polypeptides of the invention may be used sequentially as part of a multistep immunization process. For example, a mammal is initially primed with a vaccine vector of the invention such as a pox virus, *e.g.*, *via* the parenteral route, and then boosted twice with the polypeptide encoded by the vaccine vector, *e.g.*, *via* the mucosal route. In another example, liposomes associated with a polypeptide or derivative of the invention is also used for priming, with boosting being carried out mucosally using a soluble polypeptide or derivative of the invention in combination with a mucosal adjuvant (*e.g.*, LT).

A polypeptide derivative of the invention is also used in accordance with the seventh aspect as a diagnostic reagent for detecting the presence of anti-*Chlamydia* antibodies, *e.g.*, in a blood sample. Such polypeptides are about 5 to about 80, preferably about 10 to about 50 amino acids in length. They are either labeled or unlabeled, depending upon the diagnostic method. Diagnostic methods involving such a reagent are described below.

Upon expression of a DNA molecule of the invention, a polypeptide or polypeptide derivative is produced and purified using known laboratory techniques. As described above, the polypeptide or polypeptide derivative may be produced as a fusion protein containing a fused tail that facilitates purification. The fusion product is used to immunize a small mammal, *e.g.*, a mouse or a rabbit, in order to raise antibodies against the polypeptide or polypeptide derivative (monospecific antibodies). Accordingly, an eighth aspect of the invention provides a monospecific antibody that binds to a polypeptide or polypeptide derivative of the invention.

By "monospecific antibody" is meant an antibody that is capable of reacting with a unique naturally-occurring *Chlamydia* polypeptide. An antibody of the invention is either polyclonal or monoclonal. Monospecific antibodies may be recombinant, *e.g.*, chimeric (*e.g.*, constituted by a variable region of murine origin associated with a human constant region), humanized (a human immunoglobulin constant backbone together with hypervariable region of animal, *e.g.*, murine, origin), and/or single chain. Both polyclonal and monospecific antibodies may also be in the form of immunoglobulin fragments, *e.g.*, F(ab)'2 or Fab fragments. The antibodies of the invention are of any isotype, *e.g.*, IgG or IgA, and polyclonal antibodies are of a single isotype or a mixture of isotypes.

Antibodies against the polypeptides, homologs or fragments of the present invention are generated by immunization

of a mammal with a composition comprising said polypeptide, homolog or fragment. Scu antibodies may be polyclonal or monoclonal. Methods to produce polyclonal or monoclonal antibodies are well known in the art. For a review, see "Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Eds. E. Harlow and D. Lane (1988), and D.E. Yelton et al., 1981. Ann. Rev. Biochem. 50:657-680. For monoclonal antibodies, see Kohl and Milstein?...

The antibodies of the invention, which are raised to a polypeptide or polypeptide derivative of the invention, are produced and identified using standard immunological assays, *e.g.*, Western blot analysis, dot blot assay, or ELISA (see, *e.g.*, Coligan *et al.*, Current Protocols in Immunology (1994) John Wiley & Sons, Inc., New York, NY). The antibodies are used in diagnostic methods to detect the presence of a *Chlamydia* antigen in a sample, such as a biological sample. The antibodies are also used in affinity chromatography for purifying a polypeptide or polypeptide derivative of the invention. As is discussed further below, such antibodies may be used in prophylactic and therapeutic passive immunization methods.

Accordingly, a ninth aspect of the invention provides (i) a reagent for detecting the presence of *Chlamydia* in a biological sample that contains an antibody, polypeptide, or polypeptide derivative of the invention; and (ii) a diagnostic method for detecting the presence of *Chlamydia* in a biological sample, by contacting the biological sample with an antibody, a polypeptide, or a polypeptide derivative of the invention, such that an immune complex is formed, and by detecting such complex to indicate the presence of *Chlamydia* in the sample or the organism from which the sample is derived.

Those skilled in the art will readily understand that the immune complex is formed between a component of the sample and the antibody, polypeptide, or polypeptide derivative, whichever

is used, and that any unbound material is removed prior to detecting the complex. It is understood that a polypeptide reagent is useful for detecting the presence of anti-*Chlamydia* antibodies in a sample, *e.g.*, a blood sample, while an antibody of the invention is used for screening a sample, such as a gastric extract or biopsy, for the presence of *Chlamydia* polypeptides.

For diagnostic applications, the reagent (*i.e.*, the antibody, polypeptide, or polypeptide derivative of the invention) is either in a free state or immobilized on a solid support, such as a tube, a bead, or any other conventional support used in the field. Immobilization is achieved using direct or indirect means. Direct means include passive adsorption (non-covalent binding) or covalent binding between the support and the reagent. By "indirect means" is meant that an anti-reagent compound that interacts with a reagent is first attached to the solid support. For example, if a polypeptide reagent is used, an antibody that binds to it can serve as an anti-reagent, provided that it binds to an epitope that is not involved in the recognition of antibodies in biological samples. Indirect means may also employ a ligand-receptor system, for example, where a molecule such as a vitamin is grafted onto the polypeptide reagent and the corresponding receptor immobilized on the solid phase. This is illustrated by the biotin-streptavidin system. Alternatively, a peptide tail is added chemically or by genetic engineering to the reagent and the grafted or fused product immobilized by passive adsorption or covalent linkage of the peptide tail.

Such diagnostic agents may be included in a kit which also comprises instructions for use. The reagent are labeled with a detection means which allows for the detection of the reagent when it is bound to its target. The detection means may be a fluorescent agent such as fluorescein isocyanate or fluorescein isothiocyanate, or an enzyme such as horse radish

peroxidase or luciferase or alkaline phosphatase, or a radioactive element such as ^{125}I or ^{51}Cr.

Accordingly, a tenth aspect of the invention provides a process for purifying, from a biological sample, a polypeptide or polypeptide derivative of the invention, which involves carrying out antibody-based affinity chromatography with the biological sample, wherein the antibody is a monospecific antibody of the invention.

For use in a purification process of the invention, the antibody is either polyclonal or monospecific, and preferably is of the IgG type. Purified IgGs is prepared from an antiserum using standard methods (see, *e.g.*, Coligan *et al.*, *supra*). Conventional chromatography supports, as well as standard methods for grafting antibodies, are described in, *e.g.*, Antibodies: A Laboratory Manual, D. Lane, E. Harlow, Eds. (1988) and outlined below.

Briefly, a biological sample, such as an *C. pneumoniae* extract preferably in a buffer solution, is applied to a chromatography material, preferably equilibrated with the buffer used to dilute the biological sample so that the polypeptide or polypeptide derivative of the invention (*i.e.*, the antigen) is allowed to adsorb onto the material. The chromatography material, such as a gel or a resin coupled to an antibody of the invention, is in either a batch form or a column. The unbound components are washed off and the antigen is then eluted with an appropriate elution buffer, such as a glycine buffer or a buffer containing a chaotropic agent, *e.g.*, guanidine HCl, or high salt concentration (*e.g.*, 3 M $MgCl_2$). Eluted fractions are recovered and the presence of the antigen is detected, *e.g.*, by measuring the absorbance at 280 nm.

An eleventh aspect of the invention provides (i) a composition of matter comprising a monospecific antibody of the invention, together with a diluent or carrier; (ii) a pharmaceutical composition comprising a therapeutically or

prophylactically effective amount of a monospecific antibody of the invention, and (iii) a method for treating or preventing a *Chlamydia* (*e.g., C. trachomatis, C. psittaci, C. pneumoniae or C. pecorum*) infection, by administering a therapeutic or prophylactic amount of a monospecific antibody of the invention to an infected individual. Additionally, the eleventh aspect of the invention encompasses the use of a monospecific antibody of the invention in the preparation of a medicament for treating or preventing *Chlamydia* infection.

The monospecific antibody is either polyclonal or monoclonal, preferably of the IgA isotype (predominantly). In passive immunization, the antibody is administered to a mucosal surface of a mammal, *e.g.*, the gastric mucosa, *e.g.*, orally or intragastrically, advantageously, in the presence of a bicarbonate buffer. Alternatively, systemic administration, not requiring a bicarbonate buffer, is carried out. A monospecific antibody of the invention is administered as a single active component or as a mixture with at least one monospecific antibody specific for a different *Chlamydia* polypeptide. The amount of antibody and the particular regimen used are readily determined by one skilled in the art. For example, daily administration of about 100 to 1,000 mg of antibodies over one week, or three doses per day of about 100 to 1,000 mg of antibodies over two or three days, are effective regimens for most purposes.

Therapeutic or prophylactic efficacy are evaluated using standard methods in the art, *e.g.*, by measuring induction of a mucosal immune response or induction of protective and/or therapeutic immunity, using, *e.g.*, the C. *pneumoniae* mouse model. Those skilled in the art will readily recognize that the *C. pneumoniae* strain of the model may be replaced with another *Chlamydia* strain. For example, the efficacy of DNA molecules and polypeptides from *C. pneumoniae* is preferably evaluated in a mouse model using *C. pneumoniae* strain. Protection is

determined by comparing the degree of *Chlamydia* infection to that of a control group. Protection is shown when infection is reduced by comparison to the control group. Such an evaluation is made for polynucleotides, vaccine vectors, polypeptides and derivatives thereof, as well as antibodies of the invention.

Adjuvants useful in any of the vaccine compositions described above are as follows.

Adjuvants for parenteral administration include aluminum compounds, such as aluminum hydroxide, aluminum phosphate, and aluminum hydroxy phosphate. The antigen is precipitated with, or adsorbed onto, the aluminum compound according to standard protocols. Other adjuvants, such as RIBI (ImmunoChem, Hamilton, MT), is used in parenteral administration.

Adjuvants for mucosal administration include bacterial toxins, *e.g.*, the cholera toxin (CT), the *E. coli* heat-labile toxin (LT), the *Clostridium difficile* toxin A and the *pertussis* toxin (PT), or combinations, subunits, toxoids, or mutants thereof such as a purified preparation of native cholera toxin subunit B (CTB). Fragments, homologs, derivatives, and fusions to any of these toxins are also suitable, provided that they retain adjuvant activity. Preferably, a mutant having reduced toxicity is used. Suitable mutants are described, *e.g.*, in WO 95/17211 (Arg-7-Lys CT mutant), WO 96/6627 (Arg-192-Gly LT mutant), and WO 95/34323 (Arg-9-Lys and Glu-129-Gly PT mutant). Additional LT mutants that are used in the methods and compositions of the invention include, *e.g.*, Ser-63-Lys, Ala-69-Gly, Glu-110-Asp, and Glu-112-Asp mutants. Other adjuvants, such as a bacterial monophosphoryl lipid A (MPLA) of, *e.g.*, *E. coli, Salmonella minnesota, Salmonella typhimurium,* or *Shigella flexneri;* saponins, or polylactide glycolide (PLGA) microspheres, is also be used in mucosal administration.

Adjuvants useful for both mucosal and parenteral administrations include polyphosphazene (WO 95/2415), DC-chol (3

b-(N-(N',N'-dimethyl aminomethane)-carbamoyl) cholesterol; U.S. Patent No. 5,283,185 and WO 96/14831) and QS-21 (WO 88/9336).

Any pharmaceutical composition of the invention containing a polynucleotide, a polypeptide, a polypeptide derivative, or an antibody of the invention, is manufactured in a conventional manner. In particular, it is formulated with a pharmaceutically acceptable diluent or carrier, *e.g.*, water or a saline solution such as phosphate buffer saline. In general, a diluent or carrier is selected on the basis of the mode and route of administration, and standard pharmaceutical practice. Suitable pharmaceutical carriers or diluents, as well as pharmaceutical necessities for their use in pharmaceutical formulations, are described in *Remington's Pharmaceutical Sciences*, a standard reference text in this field and in the USP/NF.

The invention also includes methods in which *Chlamydia* infection are treated by oral administration of a *Chlamydia* polypeptide of the invention and a mucosal adjuvant, in combination with an antibiotic, an antacid, sucralfate, or a combination thereof. Examples of such compounds that can be administered with the vaccine antigen and the adjuvant are antibiotics, including, *e.g.*, macrolides, tetracyclines, and derivatives thereof (specific examples of antibiotics that can be used include azithromycin or doxicyclin or immunomodulators such as cytokines or steroids). In addition, compounds containing more than one of the above-listed components coupled together, are used. The invention also includes compositions for carrying out these methods, *i.e.*, compositions containing a *Chlamydia* antigen (or antigens) of the invention, an adjuvant, and one or more of the above-listed compounds, in a pharmaceutically acceptable carrier or diluent.

Amounts of the above-listed compounds used in the methods and compositions of the invention are readily determined by one skilled in the art. Treatment/immunization schedules are also

known and readily designed by one skilled in the art. For example, the non-vaccine components can be administered on days 1-14, and the vaccine antigen + adjuvant can be administered on days 7, 14, 21, and 28.

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CLAIMS

1. A nucleic acid molecule comprising a nucleic acid sequence which encodes a polypeptide selected from any of:

(a) SEQ ID Nos: 27 to 45;

(b) an immunogenic fragment comprising at least 12 consecutive amino acids from a polypeptide of (a); and

(c) a polypeptide of (a) or (b) which has been modified to improve its immunogenicity, wherein said modified polypeptide is at least 75% identical in amino acid sequence to the corresponding polypeptide of (a) or (b).

2. A nucleic acid molecule comprising a nucleic acid sequence selected from any of:

(a) SEQ ID Nos: 1 to 26;

(b) a sequence which encodes a polypeptide encoded by any one of SEQ ID Nos: 1 to 26;

(c) a sequence comprising at least 38 consecutive nucleotides from any one of the nucleic acid sequences of (a) and (b); and

(d) a sequence which encodes a polypeptide which is at least 75% identical in amino acid sequence to any one of the polypeptides encoded by SEQ ID Nos: 1 to 26.

3. A nucleic acid molecule comprising a nucleic acid sequence which encodes a fusion protein, said fusion protein comprising a polypeptide encoded by a nucleic acid molecule according to claim 1 and an additional polypeptide.

4. A nucleic acid molecule according to claim 1, operatively linked to one or more expression control sequences.

5. A vaccine comprising at least one first nucleic acid according to any one of claims 1 to 4 and a vaccine vector wherein each first nucleic acid is expressed as a polypeptide, the vaccine optionally comprising a second nucleic acid encoding an additional polypeptide which enhances the immune response to the polypeptide expressed by said first nucleic acid.

6. The vaccine of claim 5 wherein the second nucleic acid encodes an additional *Chlamydia* polypeptide.

7. A pharmaceutical composition comprising a nucleic acid according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition comprising a vaccine according to claim 5 or 6 and a pharmaceutically acceptable carrier.

9. A unicellular host transformed with the nucleic acid molecule of claim 4.

10. A nucleic acid probe of 5 to 100 nucleotides which hybridizes under stringent conditions to any one of nucleic acid molecules of SEQ ID Nos: 1 to 26, or to a homolog or complementary or anti-sense sequence of said nucleic acid molecule.

11. A primer of 10 to 40 nucleotides which hybridizes under stringent conditions to any one of nucleic acid molecules of SEQ ID Nos: 1 to 26, or to a homolog or complementary or anti-sense sequence of said nucleic acid molecule.

12. A polypeptide encoded by a nucleic acid sequence according to any one of claims 1 to 4.

13. A polypeptide comprising an amino acid sequence selected from any of:

(a) SEQ ID Nos: 27 to 45;

(b) an immunogenic fragment comprising at least 12 consecutive amino acids from a polypeptide of (a); and

(c) a polypeptide of (a) or (b) which has been modified to improve its immunogenicity, wherein said modified polypeptide is at least 75% identical in amino acid sequence to the corresponding polypeptide of (a) or (b).

14. A fusion polypeptide comprising a polypeptide of claim 12 or 13 and an additional polypeptide.

15. A method for producing a polypeptide of claim 12 or 13, comprising the step of culturing a unicellular host according to claim 9.

16. An antibody against the polypeptide of any one of claims 12 to 14.

17. A vaccine comprising at least one first polypeptide according to any one of claims 12 to 14 and a pharmaceutically acceptable carrier, optionally comprising a second polypeptide which enhances the immune response to the first polypeptide.

18. The vaccine of claim 17 wherein the second polypeptide comprises an additional *Chlamydia* polypeptide.

19. A pharmaceutical composition comprising a polypeptide according to any one of claims 12 to 14 and a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising a vaccine according to claim 17 or 18 and a pharmaceutically acceptable carrier.

21. A pharmaceutical composition comprising an antibody according to claim 16 and a pharmaceutically acceptable carrier.

22. A method for preventing or treating *Chlamydia* infection using:

(a) the nucleic acid of any one of claims 1 to 4;

(b) the vaccine of any one of claims 5, 6, 17 and 18;

(c) the pharmaceutical composition of any one of claims 7, 8, 19 to 21;

(d) the polypeptide of any one of claims 12 to 14; or

(e) the antibody of claim 16.

23. A method of detecting *Chlamydia* infection comprising the step of assaying a body fluid of a mammal to be tested, with a component selected from any one of:

(a) the nucleic acid of any one of claims 1 to 4;

(b) the polypeptide of any one of claims 12 to 14; and

(c) the antibody of claim 16.

24. A diagnostic kit comprising instructions for use and a component selected from any one of:

(a) the nucleic acid of any one of claims 1 to 4;

(b) the polypeptide of any one of claims 12 to 14; and

the antibody of claim 16.

Figure 1: CPN100397

```
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gtattggaaa gaaagcccct tgagggaaaa aaaggttgtt atg aag att cca ctc   115
                                            Met Lys Ile Pro Leu
                                              1               5

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Arg Phe Leu Leu Ile Ser Leu Val Pro Thr Leu Ser Met Ser Asn Leu
                 10                  15                  20

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             25                  30                  35

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Asp Gly Thr Asn Tyr Val Phe Lys Asp Ser Val Val Ile Glu Asn Val
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Ala Ala Asn Lys Thr Val Thr Leu Ser Gly Phe Ser Ala Leu Ser Phe
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Leu Lys Ser Pro Ala Ser Thr Val Thr Asn Gly Leu Gly Ala Ile Asn
    135                 140                 145

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150                 155                 160                 165

gac aat ttc tca aca gga gat ggc gga gca att aat tgt gca ggc tcc   643
Asp Asn Phe Ser Thr Gly Asp Gly Gly Ala Ile Asn Cys Ala Gly Ser
                170                 175                 180

ttg aag atc gca aac aat aag tcc ctt tct ttt att gga aat agt tct   691
Leu Lys Ile Ala Asn Asn Lys Ser Leu Ser Phe Ile Gly Asn Ser Ser
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Fig. 1 (con't)

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Gly Gly Glu Thr Leu Phe Gln Gly Asn Thr Ala Pro Thr Ala Ala Gly
    215                 220                 225

aaa gga ggt gct atc gcg att gca gac tct ggc acc cta tcc att tct   835
Lys Gly Gly Ala Ile Ala Ile Ala Asp Ser Gly Thr Leu Ser Ile Ser
230                 235                 240                 245

gga gac agt ggc gac att atc ttt gaa ggc aat acg ata gga gct aca   883
Gly Asp Ser Gly Asp Ile Ile Phe Glu Gly Asn Thr Ile Gly Ala Thr
                250                 255                 260

gga acc gtc tct cat agt gct att gat tta gga act agc gct aag ata   931
Gly Thr Val Ser His Ser Ala Ile Asp Leu Gly Thr Ser Ala Lys Ile
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tct gga gag aag ctc acg gag gca gaa gct aaa gat gag aag aac cgc   1123
Ser Gly Glu Lys Leu Thr Glu Ala Glu Ala Lys Asp Glu Lys Asn Arg
                330                 335                 340

act tct aaa tta ctt caa aat gtt gct ttt aaa aat ggg act gta gtt   1171
Thr Ser Lys Leu Leu Gln Asn Val Ala Phe Lys Asn Gly Thr Val Val
            345                 350                 355

tta aaa ggt gat gtc gtt tta agt gcg aac ggt ttc tct cag gat gca   1219
Leu Lys Gly Asp Val Val Leu Ser Ala Asn Gly Phe Ser Gln Asp Ala
        360                 365                 370

aac tct aag ttg att atg gat tta ggg acg tcg ttg gtt gca aac acc   1267
Asn Ser Lys Leu Ile Met Asp Leu Gly Thr Ser Leu Val Ala Asn Thr
    375                 380                 385

gaa agt atc gag tta acg aat ttg gaa att aat ata gac tct ctc agg   1315
Glu Ser Ile Glu Leu Thr Asn Leu Glu Ile Asn Ile Asp Ser Leu Arg
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Fig. 1 (con't)

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cgt ata gat cgt cct gtt gta ctg gca att agc gat gag agt ttt tat   1411
Arg Ile Asp Arg Pro Val Val Leu Ala Ile Ser Asp Glu Ser Phe Tyr
            425                 430                 435

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Gln Asn Gly Phe Leu Asn Glu Asp His Ser Tyr Asp Gly Ile Leu Glu
        440                 445                 450

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Leu Asp Ala Gly Lys Asp Ile Val Ile Ser Ala Asp Ser Arg Ser Ile
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Phe Asn Pro Thr Ala Glu Gln Glu Ala Pro Leu Val Pro Asn Leu Leu
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Gly Thr Glu Gly Ala Pro Tyr Glu Lys Arg Phe Trp Val Ala Gly Ile
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Ser Asn Val Leu His Arg Ser Gly Arg Glu Asn Gln Arg Lys Phe Arg
550                 555                 560                 565

cat gtg agt gga ggt gct gta gta ggt gct agc acg agg atg ccg ggt   1843
His Val Ser Gly Gly Ala Val Val Gly Ala Ser Thr Arg Met Pro Gly
                570                 575                 580

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Gly Asp Thr Leu Ser Leu Gly Phe Ala Gln Leu Phe Ala Arg Asp Lys
            585                 590                 595

gac tac ttt atg aat acc aat ttc gca aag acc tac gca gga tct tta   1939
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Fig. 1 (con't)

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Gly Glu Gly Gly Leu Arg Glu Ile Leu Leu Pro Tyr Val Ser Lys Thr
630                 635                 640                 645

ctg ccg tgc tct ttc tat ggg cag ctt agc tac ggc cat acg gat cat   2083
Leu Pro Cys Ser Phe Tyr Gly Gln Leu Ser Tyr Gly His Thr Asp His
                650                 655                 660

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Arg Val Ala Val Glu Asn Thr Ser Gly Arg Gly Phe Phe Gln Glu Tyr
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Asn Leu Ala Ile Pro Leu Gly Ile Lys Leu Glu Lys Arg Phe Ala Glu
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caa tat tat cat gtt gta gcg atg tat tct cca gat gtt tgt cgt agt   2419
Gln Tyr Tyr His Val Val Ala Met Tyr Ser Pro Asp Val Cys Arg Ser
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acc aaa ggt tcg aac tta gca aga cag gct ggt att gtt cag gcc tca   2515
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790                 795                 800                 805

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Fig. 1 (con't)

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aaa atc aaa ttt tagcgatttc tctttcgatg ctatttttcc atggctattt       2663
Lys Ile Lys Phe
        840

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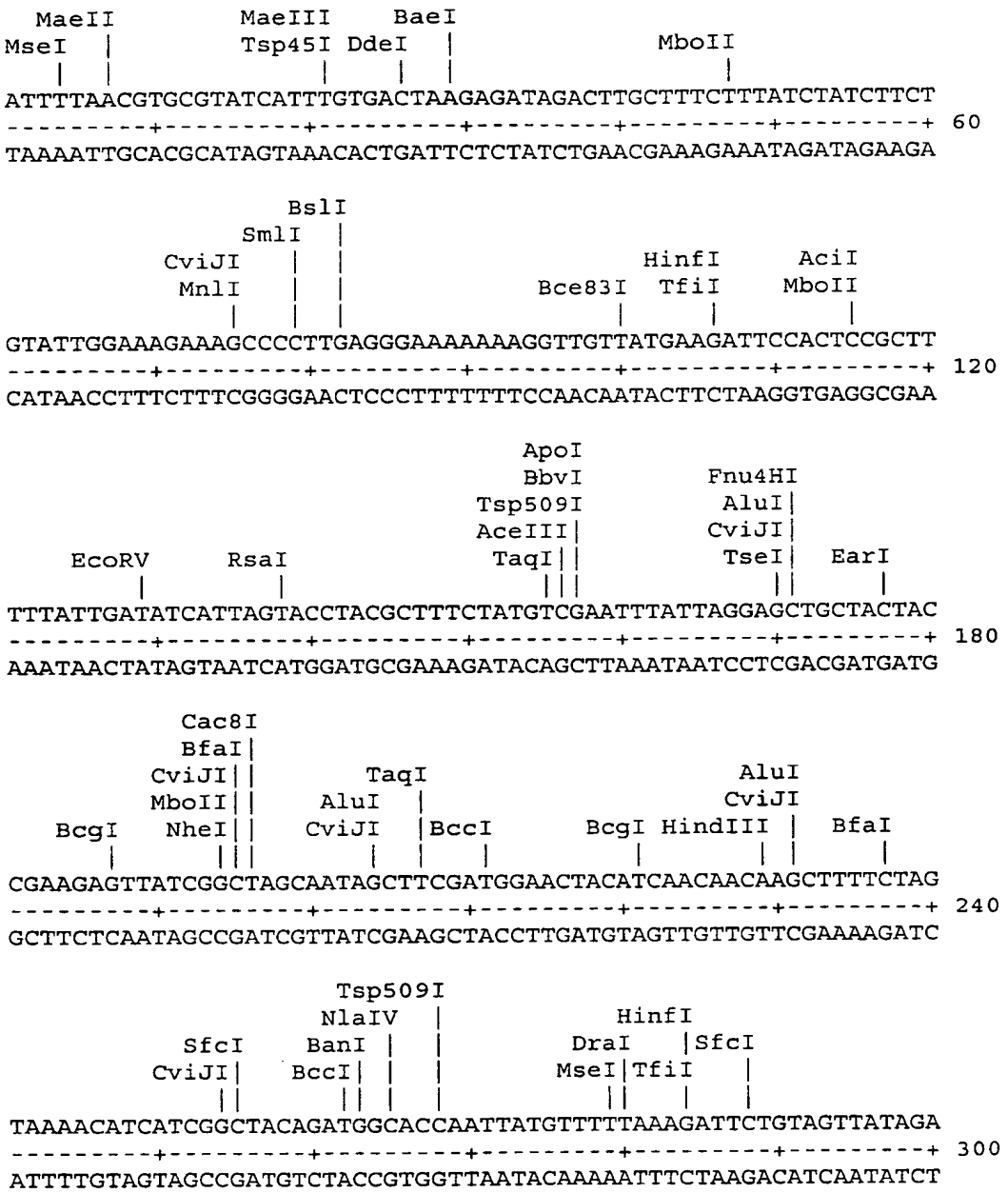
Figure 2 (RY-32)

Restriction Enzyme analysis of CPN100397



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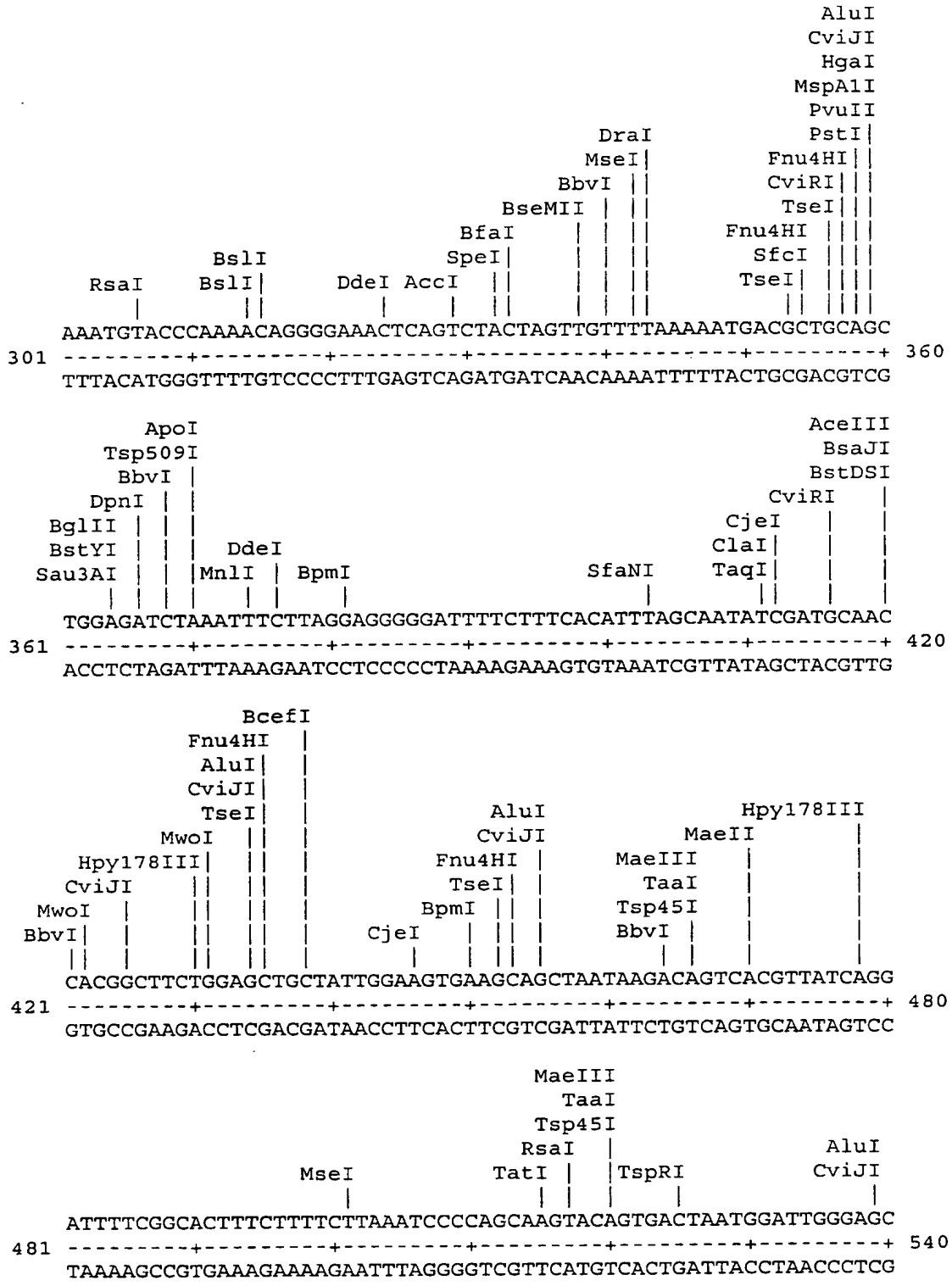
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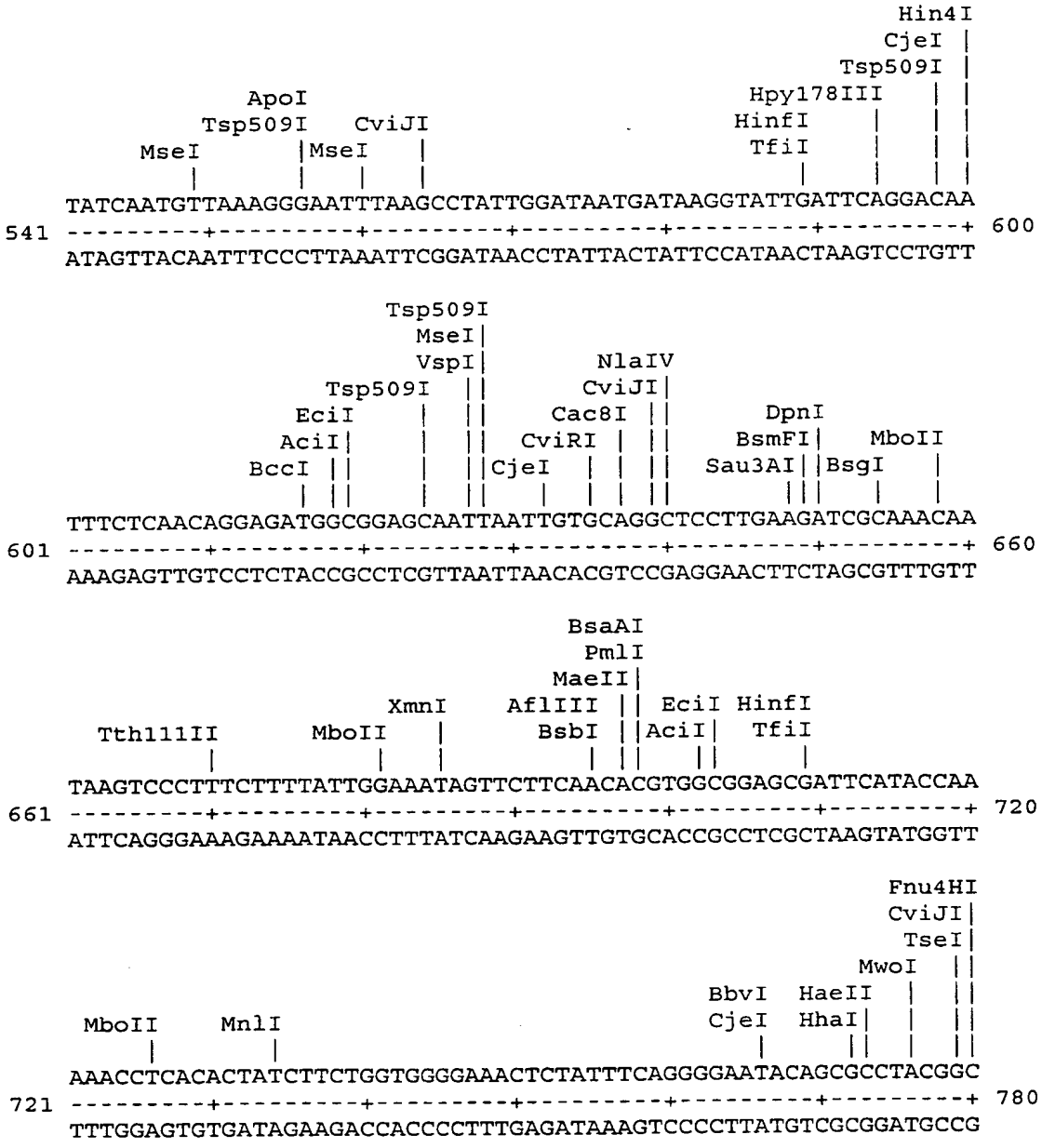
Fig. 2 (con't)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BccI
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Fig. 2 (con't)

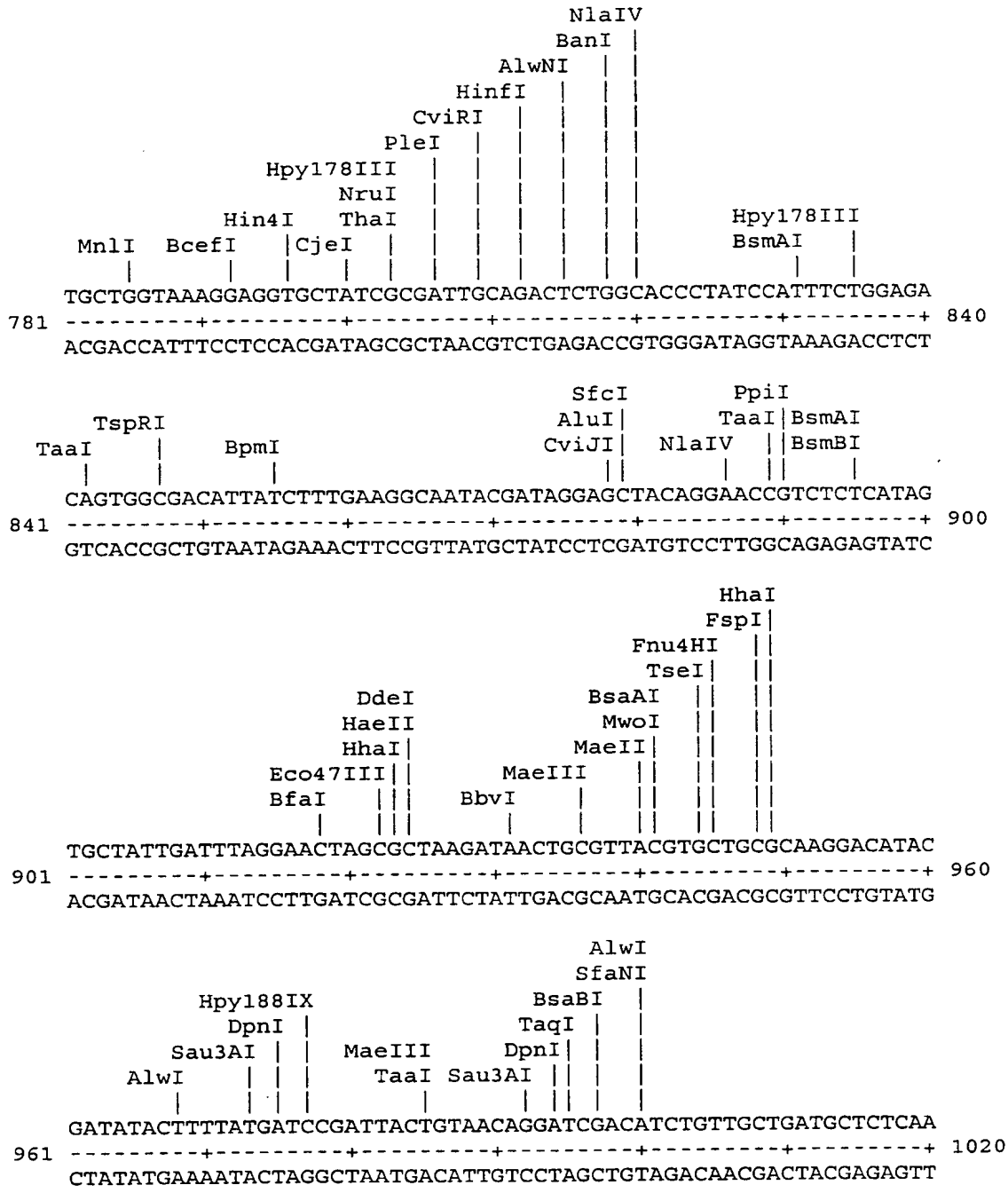
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Fig. 2 (con't)

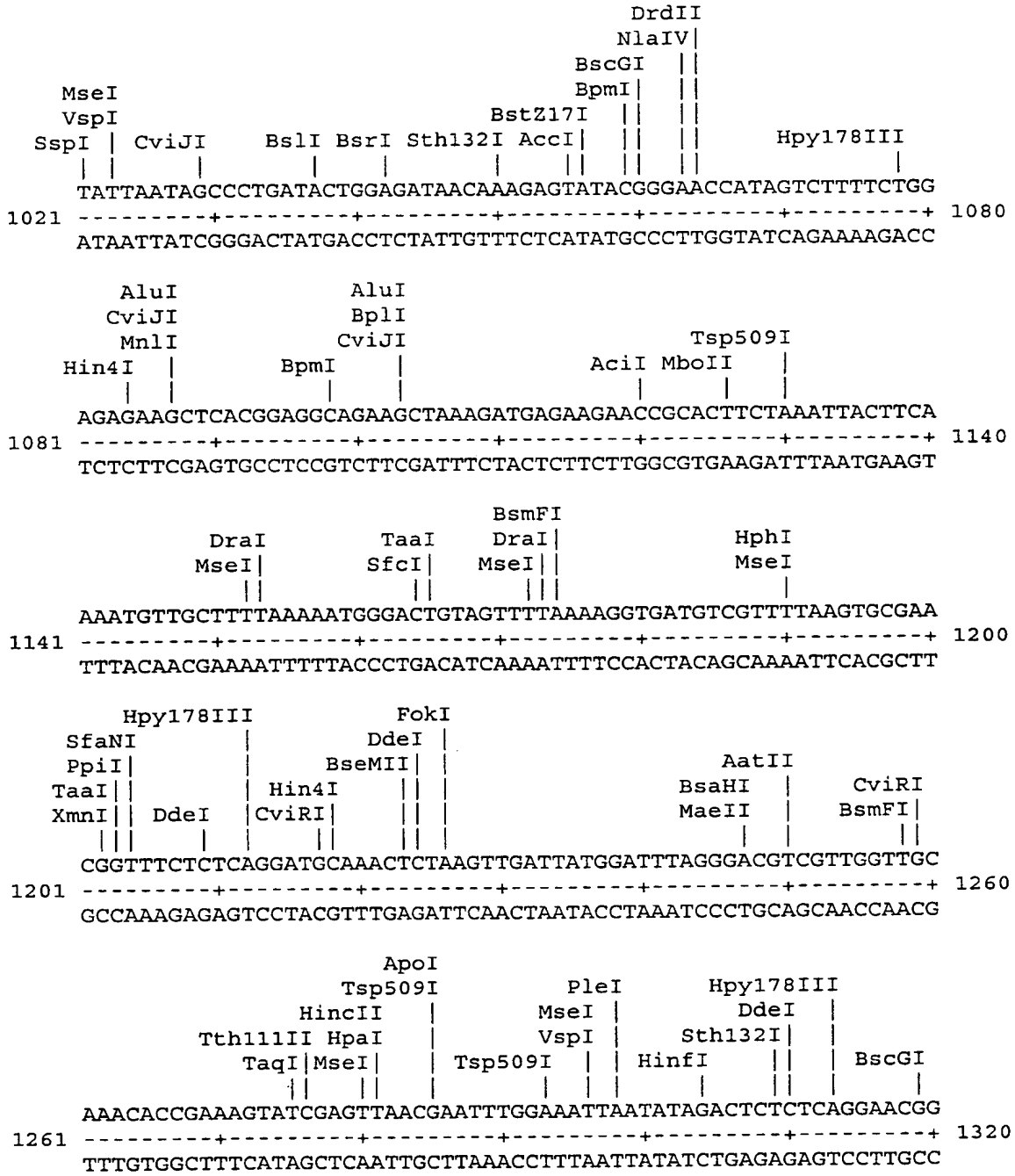
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Fig. 2 (con't)

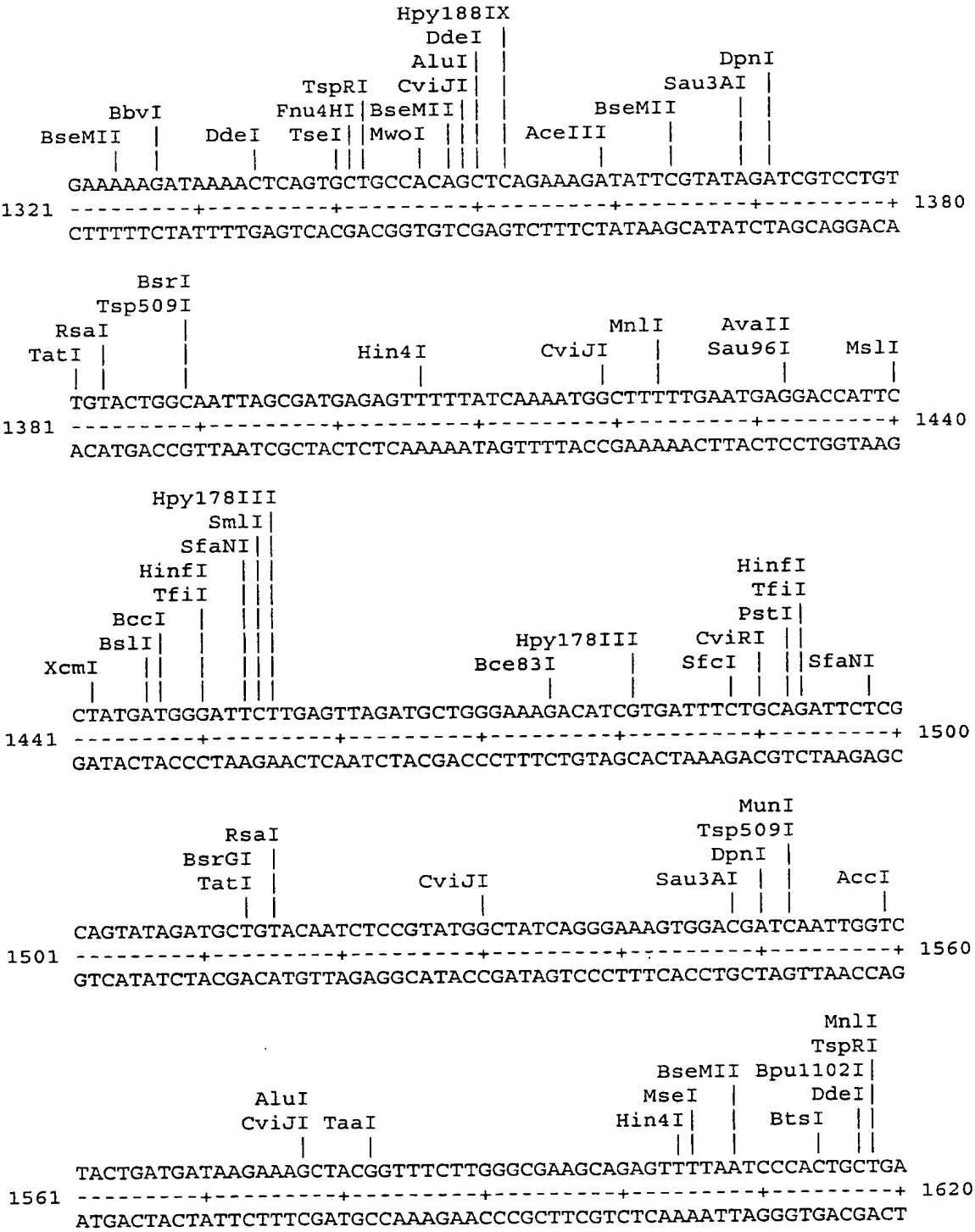
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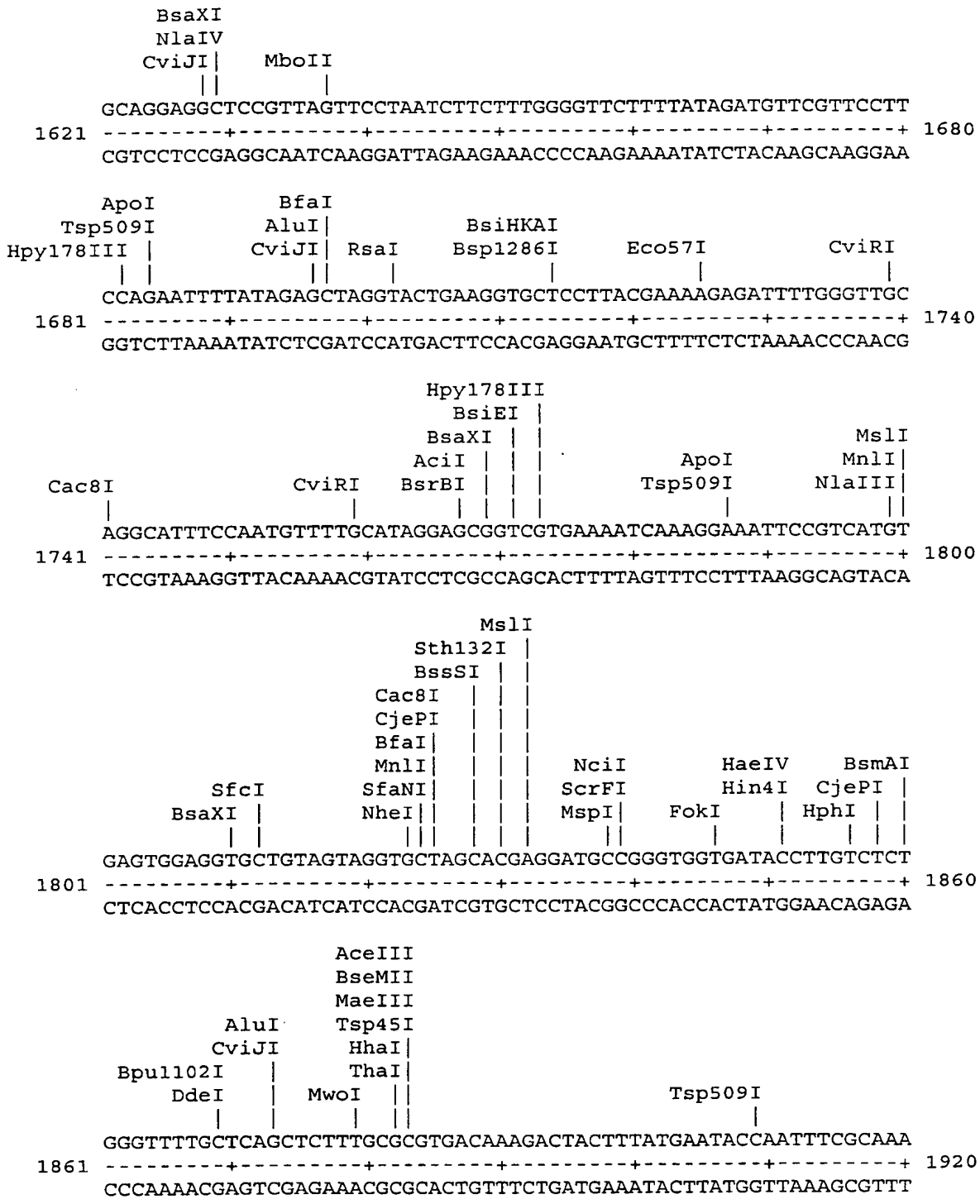
Fig. 2 (con't)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RsaI
BsiHKAI
Bsp1286I
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1740
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BsaXI
AciI
BsrBI
ApoI
Tsp509I
MslI
MnlI
NlaIII
Cac8I
CviRI
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1741
1800
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BssSI
Cac8I
CjePI
BfaI
MnlI
NciI
ScrFI
MspI
HaeIV
Hin4I
FokI
BsmAI
CjePI
HphI
SfcI
SfaNI
NheI
BsaXI
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MaeIII
AluI
CviJI
Tsp45I
HhaI
ThaI
Bpu1102I
DdeI
MwoI
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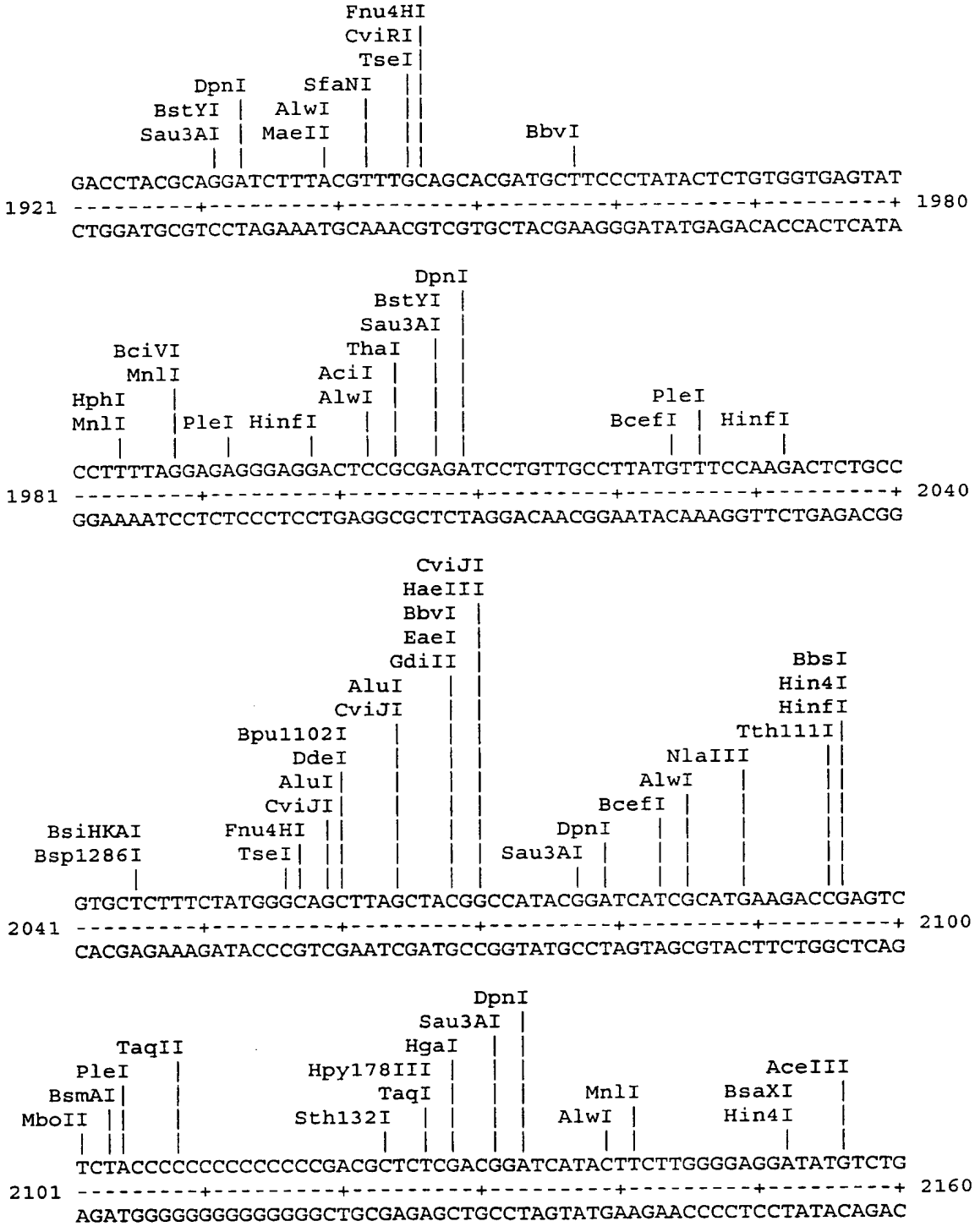
Fig. 2 (con't)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Sau3AI
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HgaI
PleI
Hpy178III
AceIII
BsmAI
TaqI
MnlI
BsaXI
MboII
Sth132I
AlwI
Hin4I
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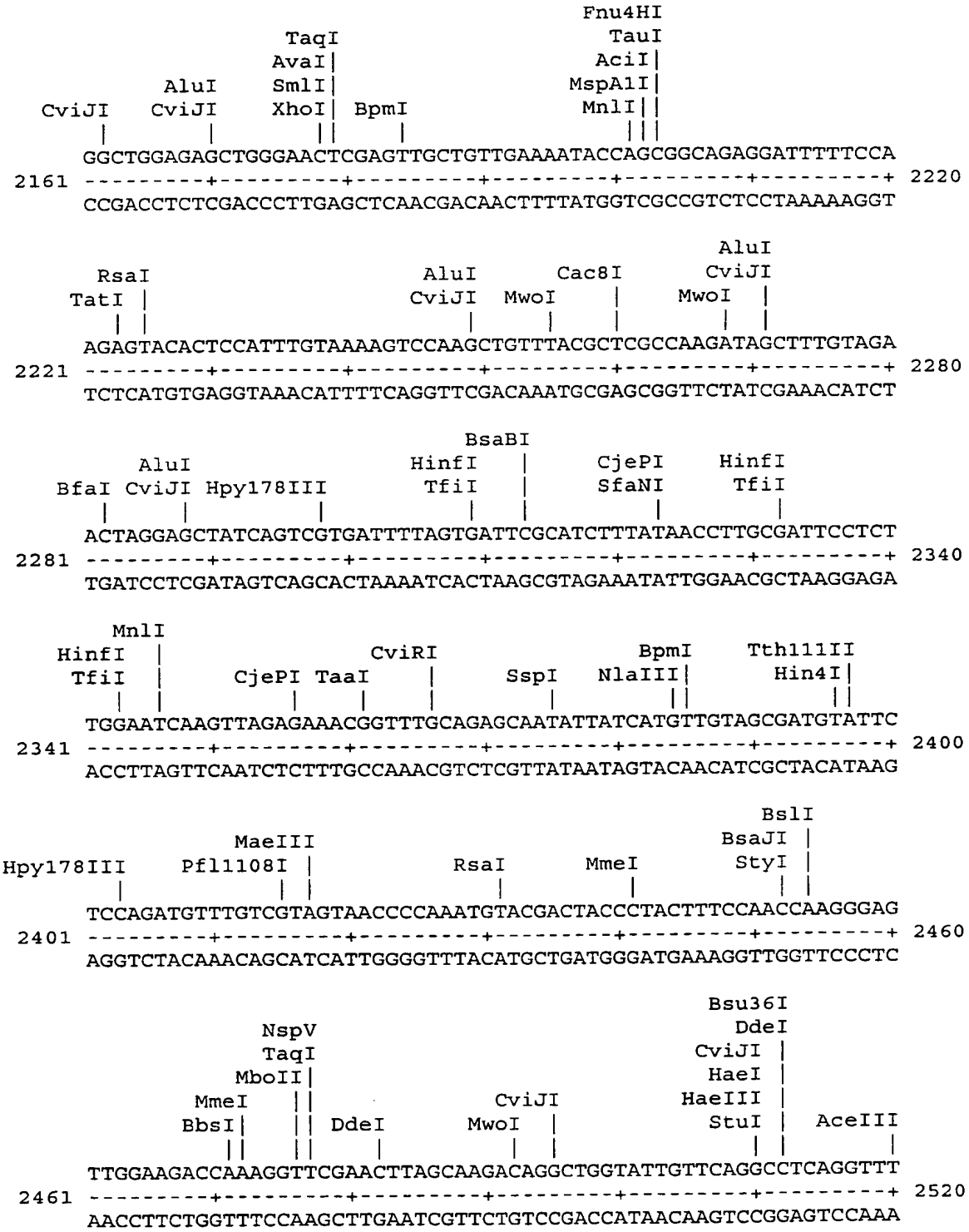
Fig. 2 (con't)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MnlI
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AluI
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CviJI
TatI
CviJI
MwoI
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AluI
HinfI
CjePI
HinfI
BfaI
CviJI
Hpy178III
TfiI
SfaNI
TfiI
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BpmI
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TfiI
CjePI
TaaI
SspI
NlaIII
Hin4I
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MmeI
StyI
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HaeIII
BbsI
DdeI
MwoI
StuI
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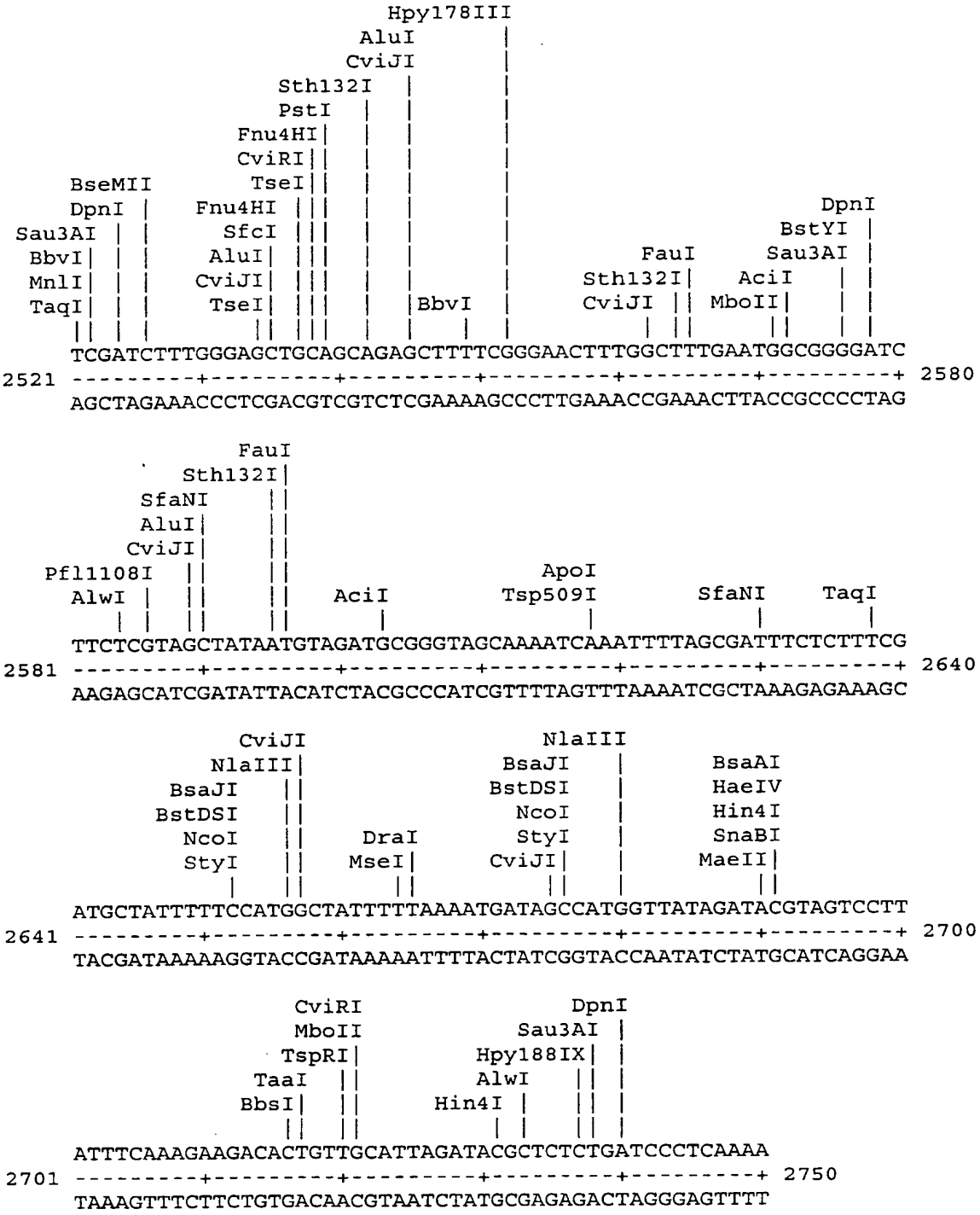
Fig. 2 (con't)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TseI
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SfcI
BbvI
AluI
MnlI
CviJI
TaqI
TseI
BbvI
DpnI
BstYI
FauI
Sau3AI
Sth132I
AciI
CviJI
MboII
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2521 ---------+---------+---------+---------+---------+---------+ 2580
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FauI
Sth132I
SfaNI
AluI
CviJI
Pfl1108I
AlwI
AciI
ApoI
Tsp509I
SfaNI
TaqI
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NlaIII
BsaJI
BstDSI
NcoI
StyI
DraI
MseI
NlaIII
BsaJI
BstDSI
NcoI
StyI
CviJI
BsaAI
HaeIV
Hin4I
SnaBI
MaeII
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MboII
TspRI
TaaI
BbsI
DpnI
Sau3AI
Hpy188IX
AlwI
Hin4I
ATTTCAAAGAAGACACTGTTGCATTAGATACGCTCTCTGATCCCTCAAAA
2701 ---------+---------+---------+---------+---------+ 2750
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Figure 3: CPN100421

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                                            Met Pro Pro Leu Asn
                                              1               5

gct gat gat gtt ctc cct aga gac cat ctg tca gat gga agt ttc tca   163
Ala Asp Asp Val Leu Pro Arg Asp His Leu Ser Asp Gly Ser Phe Ser
                 10                  15                  20

gat acg tat cca gac att aca acg caa gcg atc atc tta att ttc ttg   211
Asp Thr Tyr Pro Asp Ile Thr Thr Gln Ala Ile Ile Leu Ile Phe Leu
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gcc cta tcg cct ttc ctg gtc atg ttg ctc act tcg tat cta aag att   259
Ala Leu Ser Pro Phe Leu Val Met Leu Leu Thr Ser Tyr Leu Lys Ile
         40                  45                  50

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     55                  60                  65

cct ccc agt caa gtc ctc aat ggg att gca ctc atc cta tct att tat   355
Pro Pro Ser Gln Val Leu Asn Gly Ile Ala Leu Ile Leu Ser Ile Tyr
 70                  75                  80                  85

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Val Met Phe Pro Thr Gly Val Ala Met Tyr Lys Asp Ala Arg Lys Glu
                 90                  95                 100

atc gaa gcc aat acc att cct caa agc ctc ttc act gca gaa ggt gct   451
Ile Glu Ala Asn Thr Ile Pro Gln Ser Leu Phe Thr Ala Glu Gly Ala
            105                 110                 115

gaa aca gtg ttt gtc gct tta aac aaa tct aaa gaa cct ttg cgc tct   499
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                170                 175                 180

aat gct ttc gaa att gga gtc ttg atc tat cta cct ttc ttt gtt att   691
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Fig. 3 (con't)

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    215                 220                 225

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230                 235                 240                 245

taaggacacg tgccgtgtta gcatttttcg caactagttt caaatctgtt ctttttgagt 895

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Figure 4 (RY-34)

Restriction enzyme analysis of CP100421

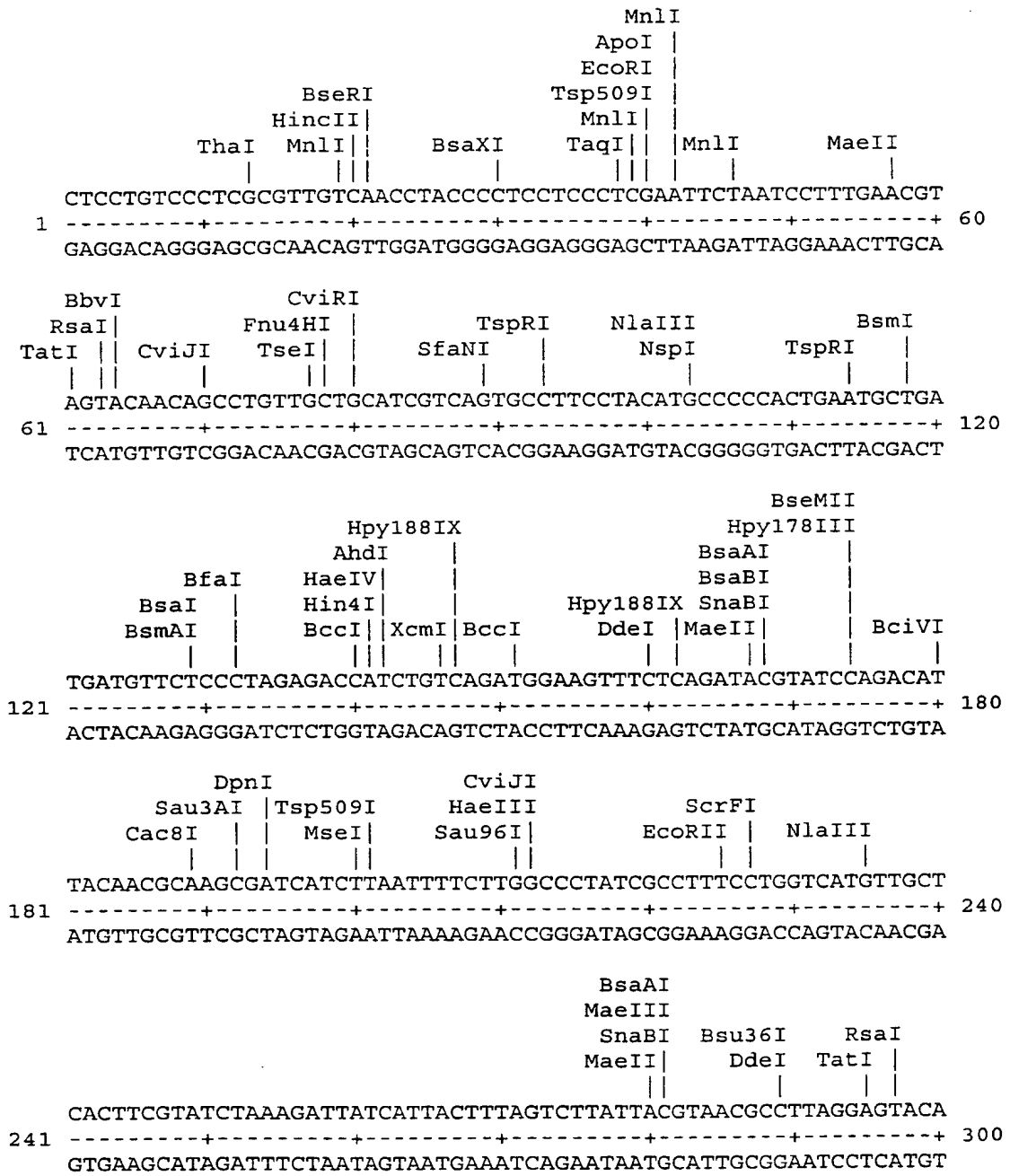
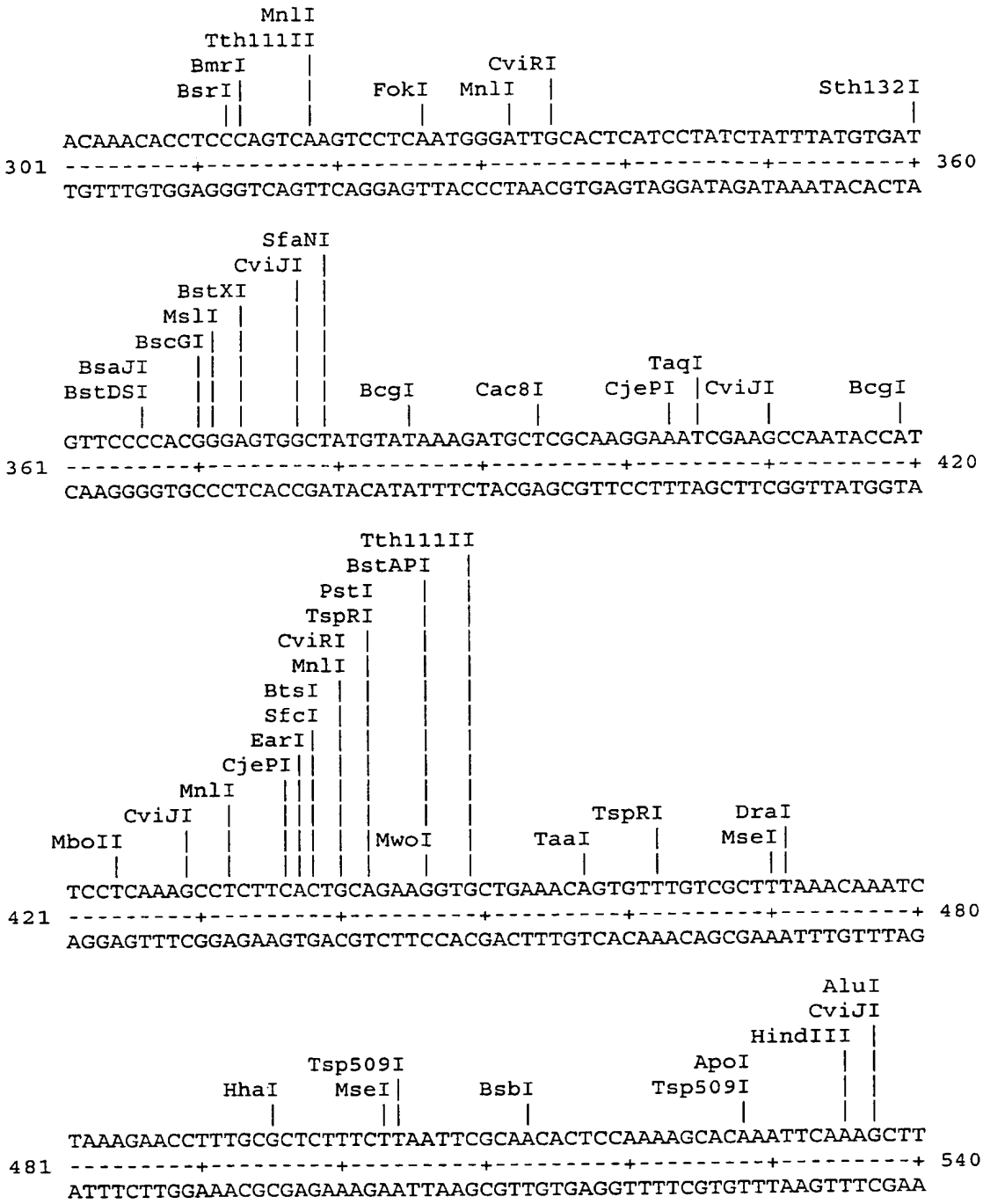


Fig. 4 (con't)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301
360
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CviJI
BstXI
MslI
BscGI
BsaJI
BstDSI
TaqI
BcgI
Cac8I
CjePI
CviJI
BcgI
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PstI
TspRI
CviRI
MnlI
BtsI
SfcI
EarI
CjePI
MnlI
CviJI
MboII
MwoI
TaaI
TspRI
DraI
MseI
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CviJI
HindIII
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ApoI
HhaI
MseI
BsbI
Tsp509I
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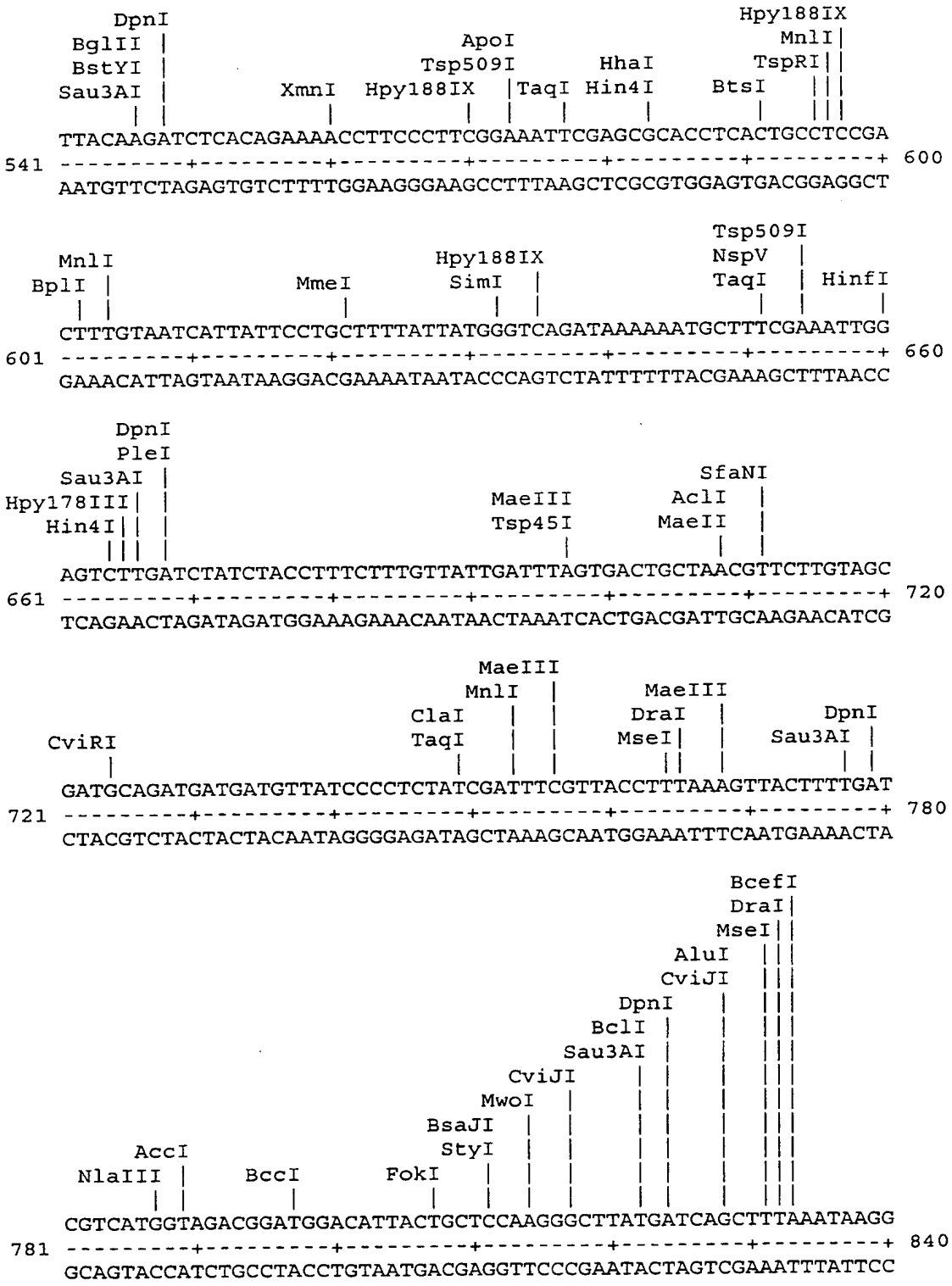
Fig. 4 (con't)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AclI
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AluI
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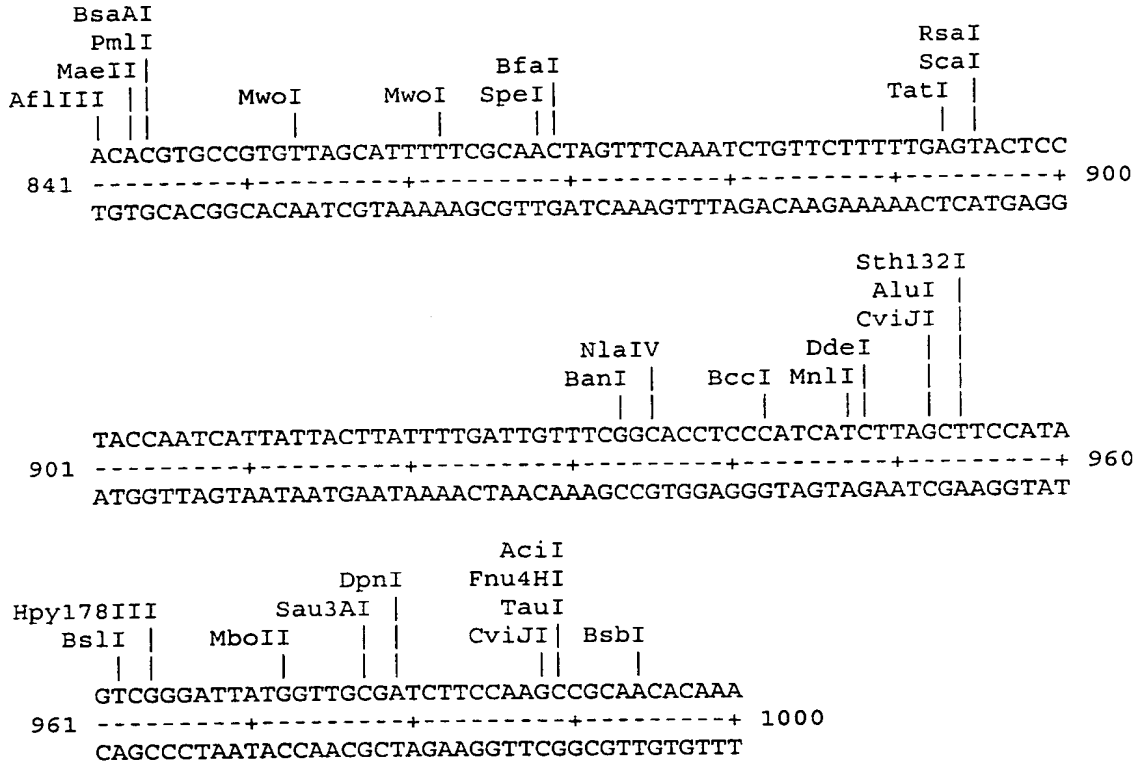
Fig. 4 (con't)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AluI
CviJI
NlaIV
BanI
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DdeI
MnlI
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DpnI
Fnu4HI
Hpy178III
Sau3AI
TauI
BslI
MboII
CviJI
BsbI
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Figure 5:

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                                            Met Lys Phe Phe Ser
                                              1               5

tta att ttt aaa gat gat gat gtc tcc cca aat aag aag gtt tta tct   163
Leu Ile Phe Lys Asp Asp Asp Val Ser Pro Asn Lys Lys Val Leu Ser
                 10                  15                  20

cct gaa gct ttc tct gct ttc ctt gat gcc aaa gag ctg tta gaa aaa   211
Pro Glu Ala Phe Ser Ala Phe Leu Asp Ala Lys Glu Leu Leu Glu Lys
             25                  30                  35

aca aaa gcc gat agc gaa gcc tat gtt gca gag aca gaa caa aag tgt   259
Thr Lys Ala Asp Ser Glu Ala Tyr Val Ala Glu Thr Glu Gln Lys Cys
         40                  45                  50

gca caa att cgt caa gaa gct aaa gat caa gga ttt aaa gag gga tct   307
Ala Gln Ile Arg Gln Glu Ala Lys Asp Gln Gly Phe Lys Glu Gly Ser
     55                  60                  65

gaa tcc tgg agc aag caa att gct ttc tta gaa gaa gaa act aaa aat   355
Glu Ser Trp Ser Lys Gln Ile Ala Phe Leu Glu Glu Glu Thr Lys Asn
 70                  75                  80                  85

cta cgc ata aga gta cgc gag gcc ttg gtt cct ctg gca att gcg agt   403
Leu Arg Ile Arg Val Arg Glu Ala Leu Val Pro Leu Ala Ile Ala Ser
                 90                  95                 100

gtg agg aaa atc att ggg aag gaa ctc gaa tta cat cct gaa act att   451
Val Arg Lys Ile Ile Gly Lys Glu Leu Glu Leu His Pro Glu Thr Ile
            105                 110                 115

gtc tct att att tct caa gca ttg aaa gag ctc aca caa aat aaa cat   499
Val Ser Ile Ile Ser Gln Ala Leu Lys Glu Leu Thr Gln Asn Lys His
        120                 125                 130

atc att atc tct gtc aat ccc aaa gat tta cct ctt gtt gag aaa agt   547
Ile Ile Ile Ser Val Asn Pro Lys Asp Leu Pro Leu Val Glu Lys Ser
    135                 140                 145

cgt cct gaa ctc aag aac atc gtg gag tat gct gac tcc tta att ctt   595
Arg Pro Glu Leu Lys Asn Ile Val Glu Tyr Ala Asp Ser Leu Ile Leu
150                 155                 160                 165

aca gca aaa cct gat gtt act cct ggg ggt tgc att atc gag act gaa   643
Thr Ala Lys Pro Asp Val Thr Pro Gly Gly Cys Ile Ile Glu Thr Glu
                170                 175                 180

gca ggg atc atc aat gcg cag ctt gat gta caa tta gat gcc tta gaa   691
Ala Gly Ile Ile Asn Ala Gln Leu Asp Val Gln Leu Asp Ala Leu Glu
            185                 190                 195
```

Fig. 5 (con't)

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tct gag act tca tca tcc acg gat tct tct tct tta tct aat gat cag   787
Ser Glu Thr Ser Ser Ser Thr Asp Ser Ser Ser Leu Ser Asn Asp Gln
    215                 220                 225

gat aag aaa gaa taaaggtatt cactattatg cgatccattt ttcgattttc       839
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230

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Figure 6 (RY-35)

Restriction analysis of CPN100422

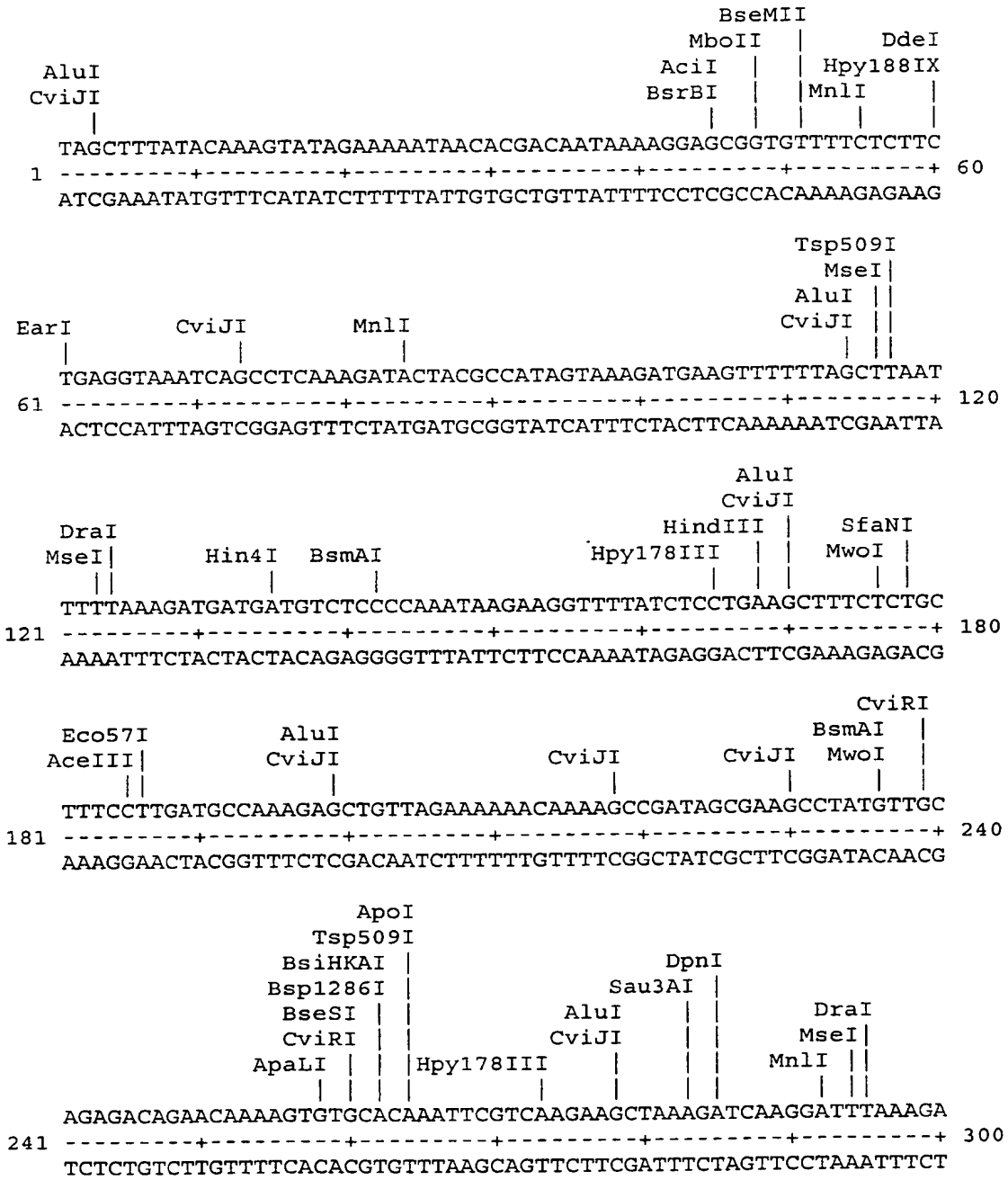
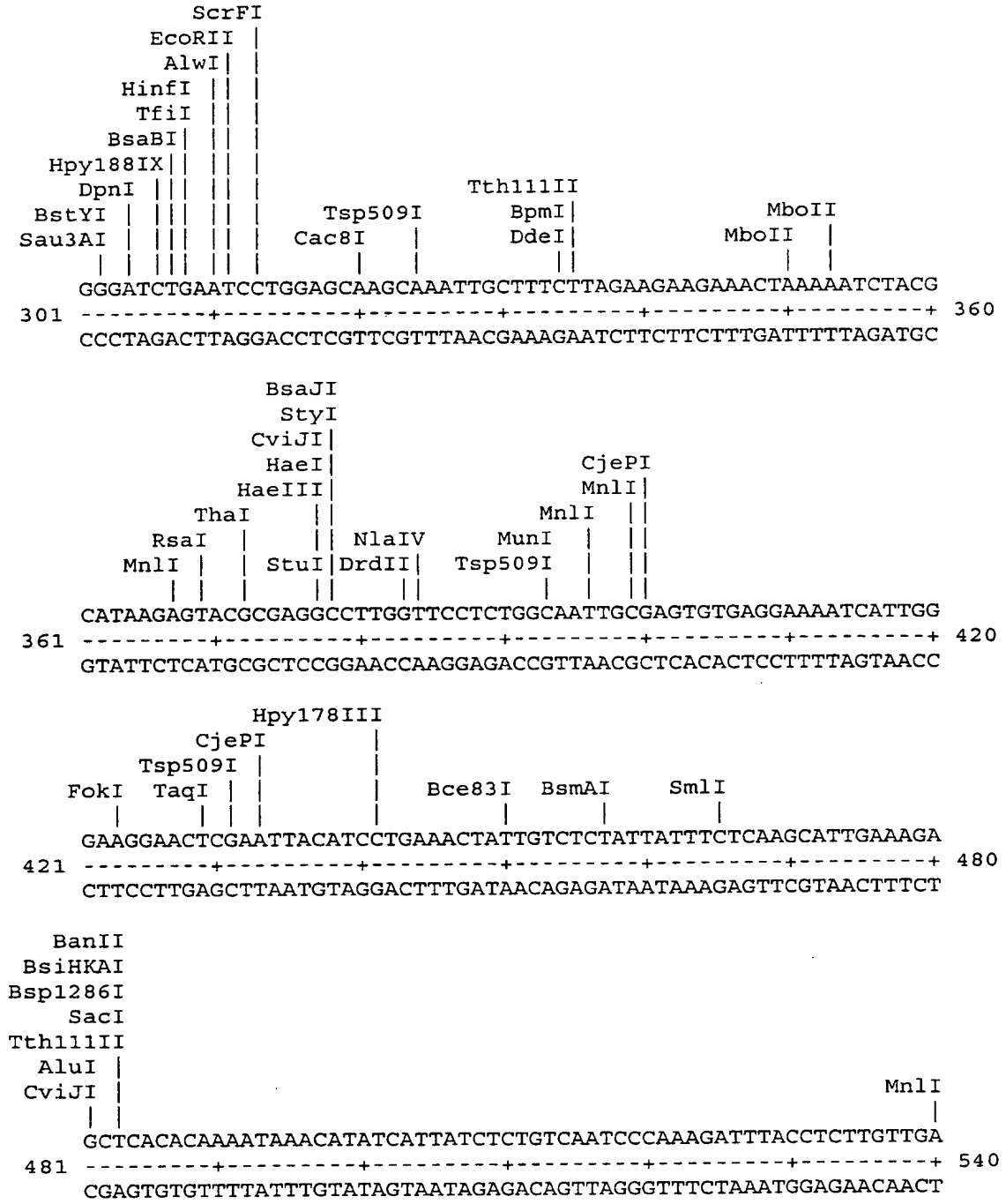


Fig. 6 (con't)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CviJI
HaeI
HaeIII
ThaI
RsaI
MnlI
NlaIV
StuI
DrdII
MunI
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Bsp1286I
SacI
Tth111II
AluI
CviJI
MnlI
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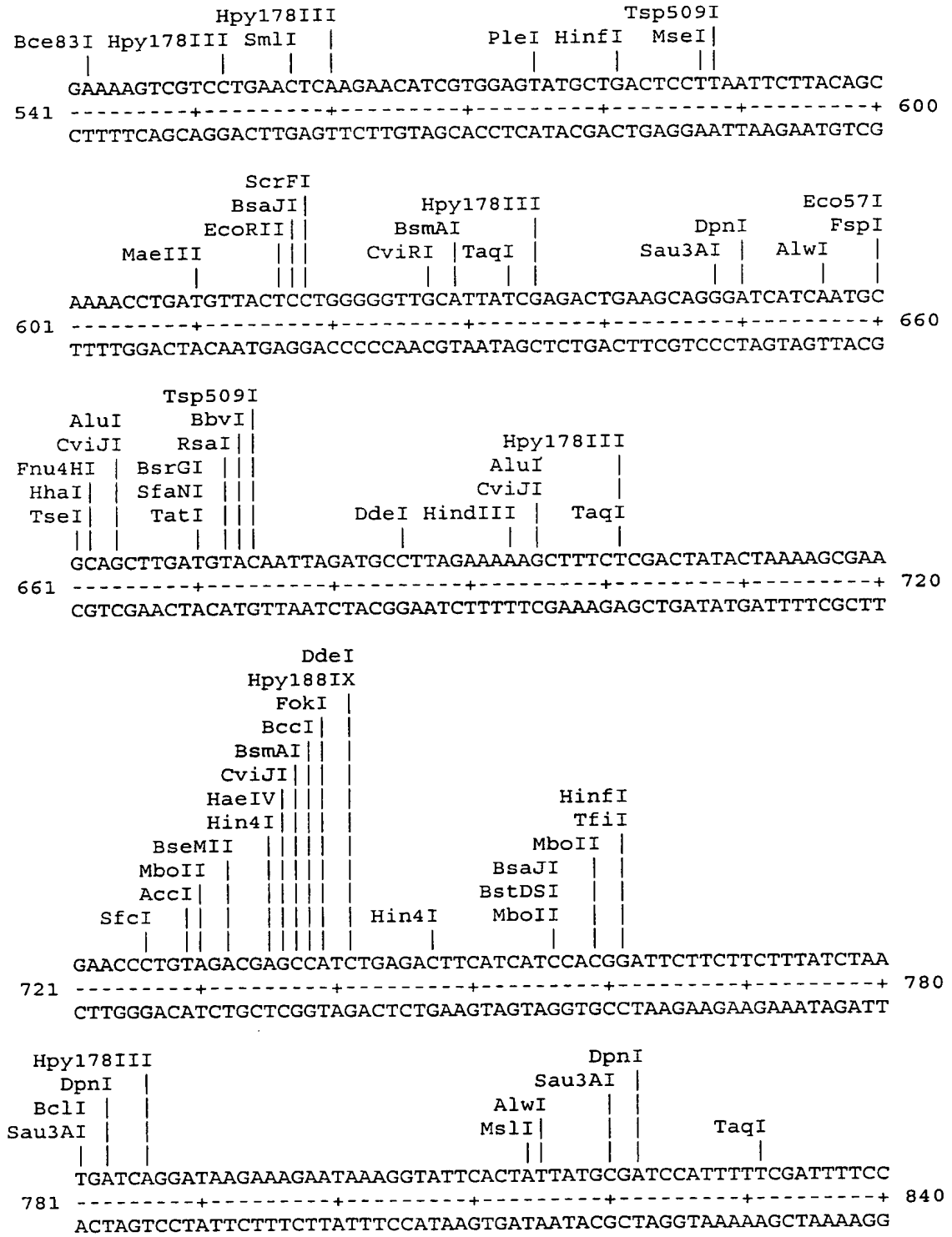
Fig. 6 (con't)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MaeIII
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CviRI
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DpnI
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HhaI
SfaNI
TseI
TatI
Hpy178III
AluI
CviJI
DdeI
HindIII
TaqI
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FokI
BccI
BsmAI
CviJI
HaeIV
Hin4I
BseMII
MboII
AccI
SfcI
Hin4I
HinfI
TfiI
MboII
BsaJI
BstDSI
MboII
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DpnI
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AlwI
MslI
TaqI
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Fig. 6 (con't)

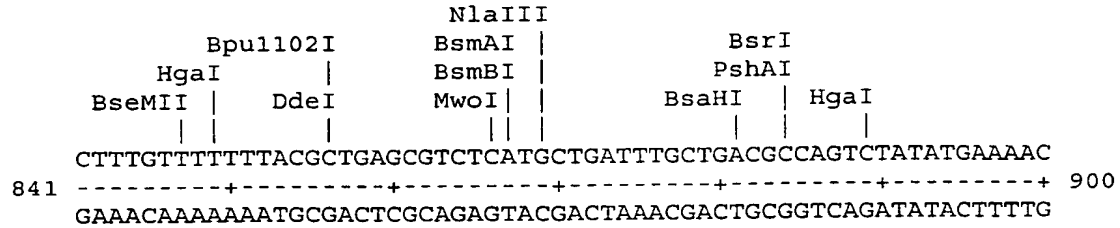
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Figure 7: CPN 100424

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Cys Thr Ser Cys Asn Ser Arg Ser Leu Ile Val His Gly Leu Pro Gly
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gaa aaa atc cgt tat caa gaa ggc tta tca gaa cag atg gcc tct acg   451
Glu Lys Ile Arg Tyr Gln Glu Gly Leu Ser Glu Gln Met Ala Ser Thr
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att aga aaa atg gat ggc gtt gtc gat gcc tca gta cag att tcc ttc   499
Ile Arg Lys Met Asp Gly Val Val Asp Ala Ser Val Gln Ile Ser Phe
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Fig. 7 (con't)

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Val Leu Ile Leu Ile Leu Phe Val Ile Ser Cys Gly Leu Leu Trp Val
230                 235                 240                 245

att tgg aaa act cat act ctc att atg act atg gga ggt aca aaa ggg   883
Ile Trp Lys Thr His Thr Leu Ile Met Thr Met Gly Gly Thr Lys Gly
                250                 255                 260

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Phe Phe Asn Pro Thr Pro Tyr Thr Lys Asn Ala Leu Glu Ala Lys Lys
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gcc gag gga gca gct gct gac aaa gag aaa aaa gaa gat gca gat tca   979
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cag ggg gaa agc aaa aat gcg gaa acc agt gat aaa gac tct agt gat   1027
Gln Gly Glu Ser Lys Asn Ala Glu Thr Ser Asp Lys Asp Ser Ser Asp
    295                 300                 305

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Figure 8 (RY-36)

Restriction analysis of CPN100424

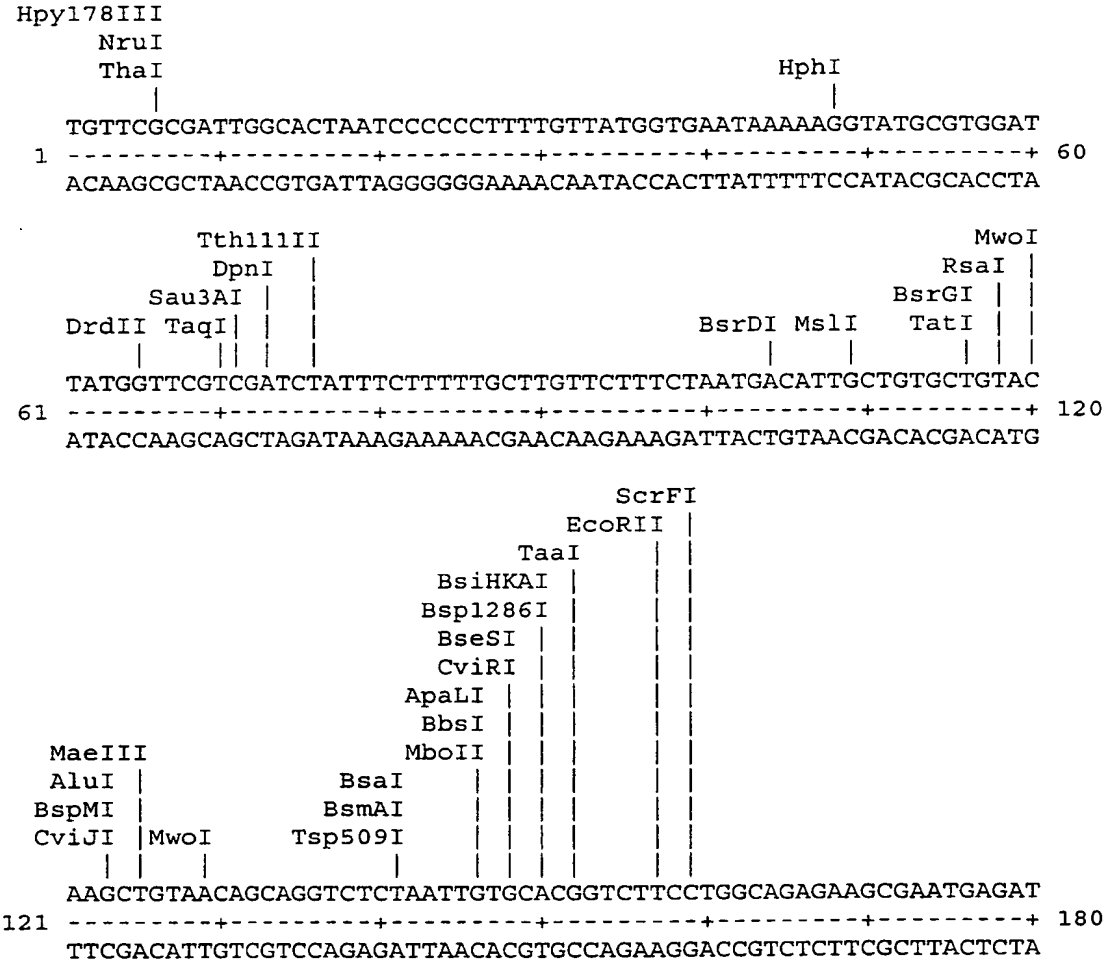
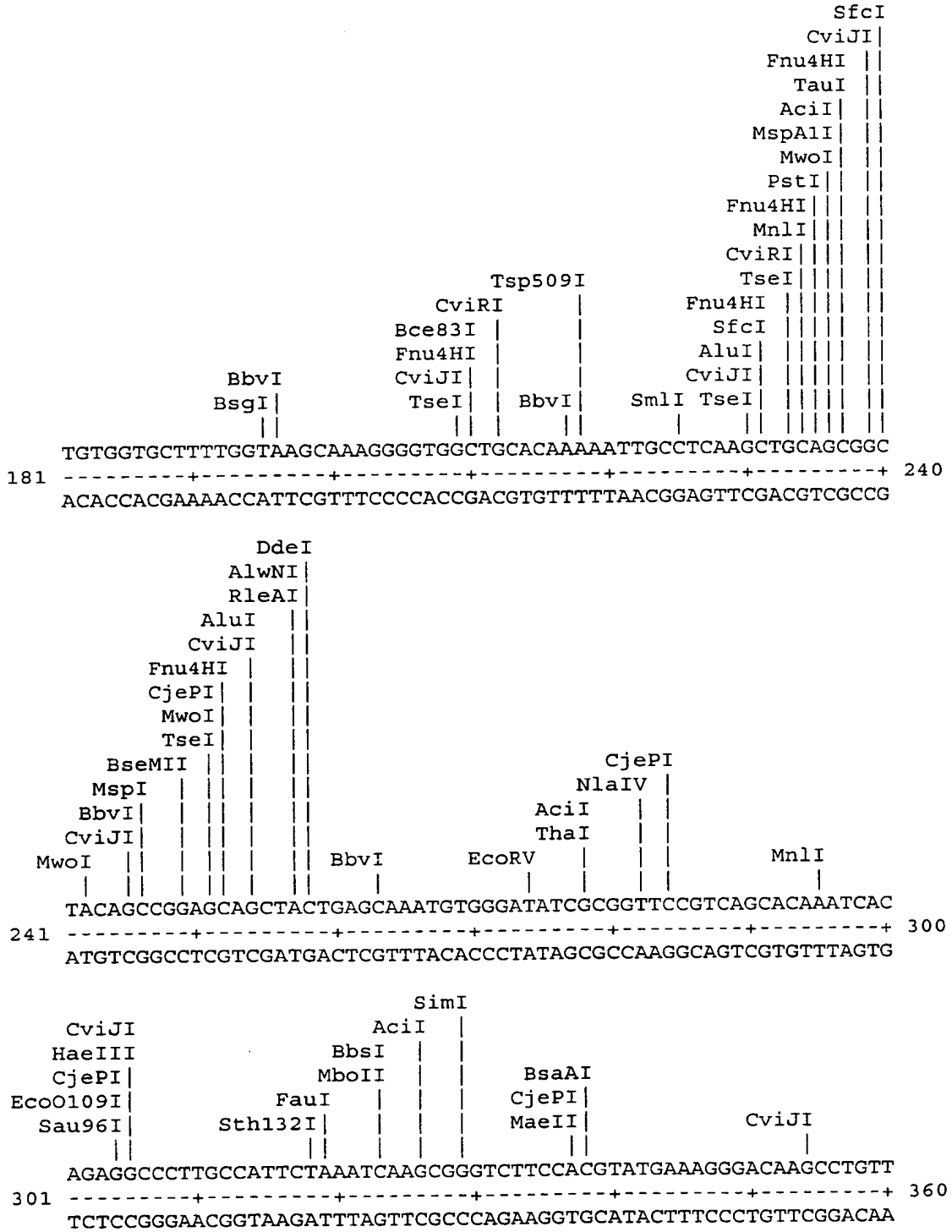


Fig. 8 (con't)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AciI
ThaI
MnlI
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CviJI
AciI
HaeIII
BbsI
CjePI
MboII
BsaAI
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FauI
CjePI
Sau96I
Sth132I
MaeII
CviJI
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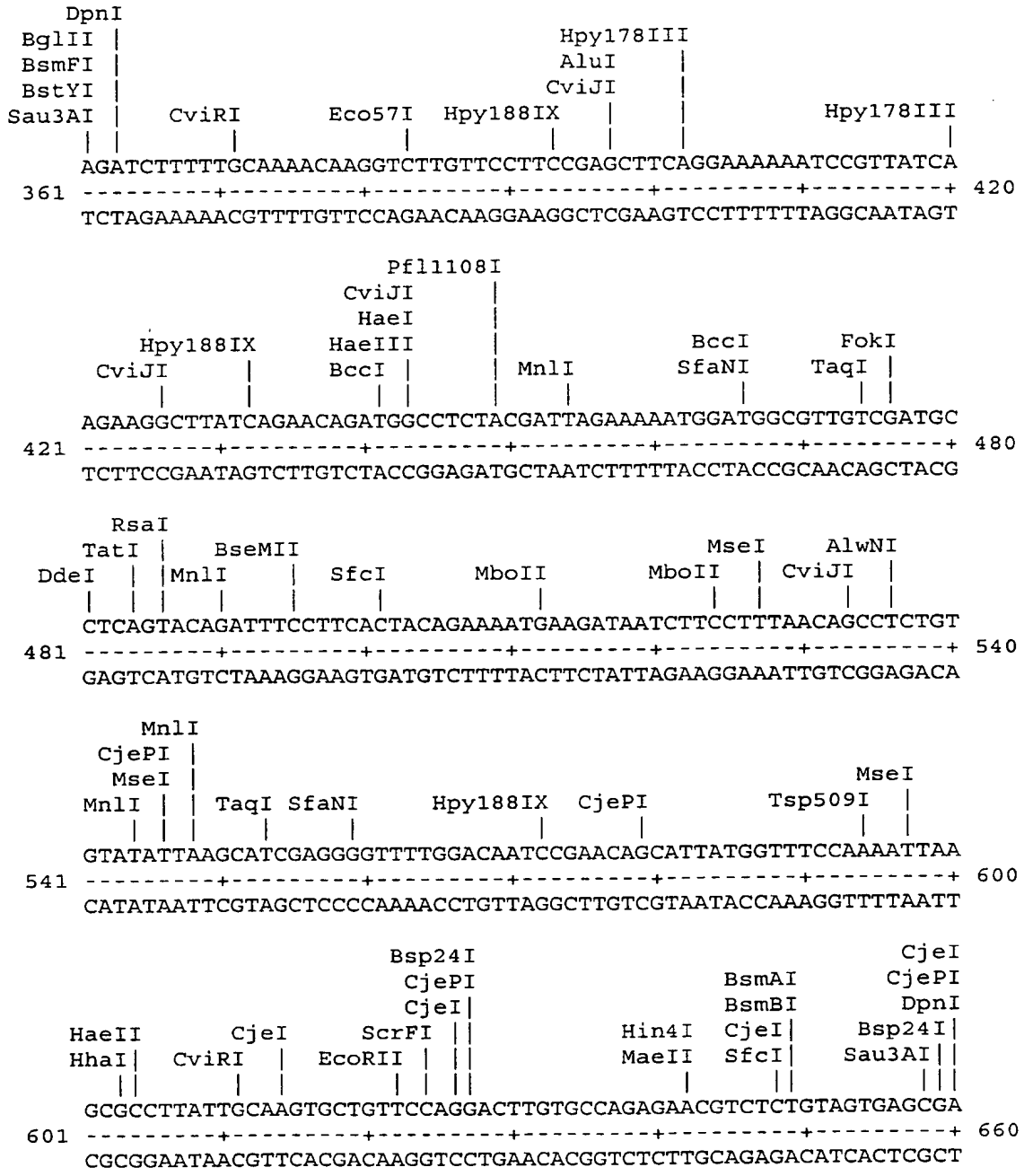
Fig. 8 (con't)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DdeI
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CviJI
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MnlI
TaqI
SfaNI
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CjePI
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BsmBI
DpnI
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HhaI
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CjeI
EcoRII
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Hin4I
MaeII
CjeI
SfcI
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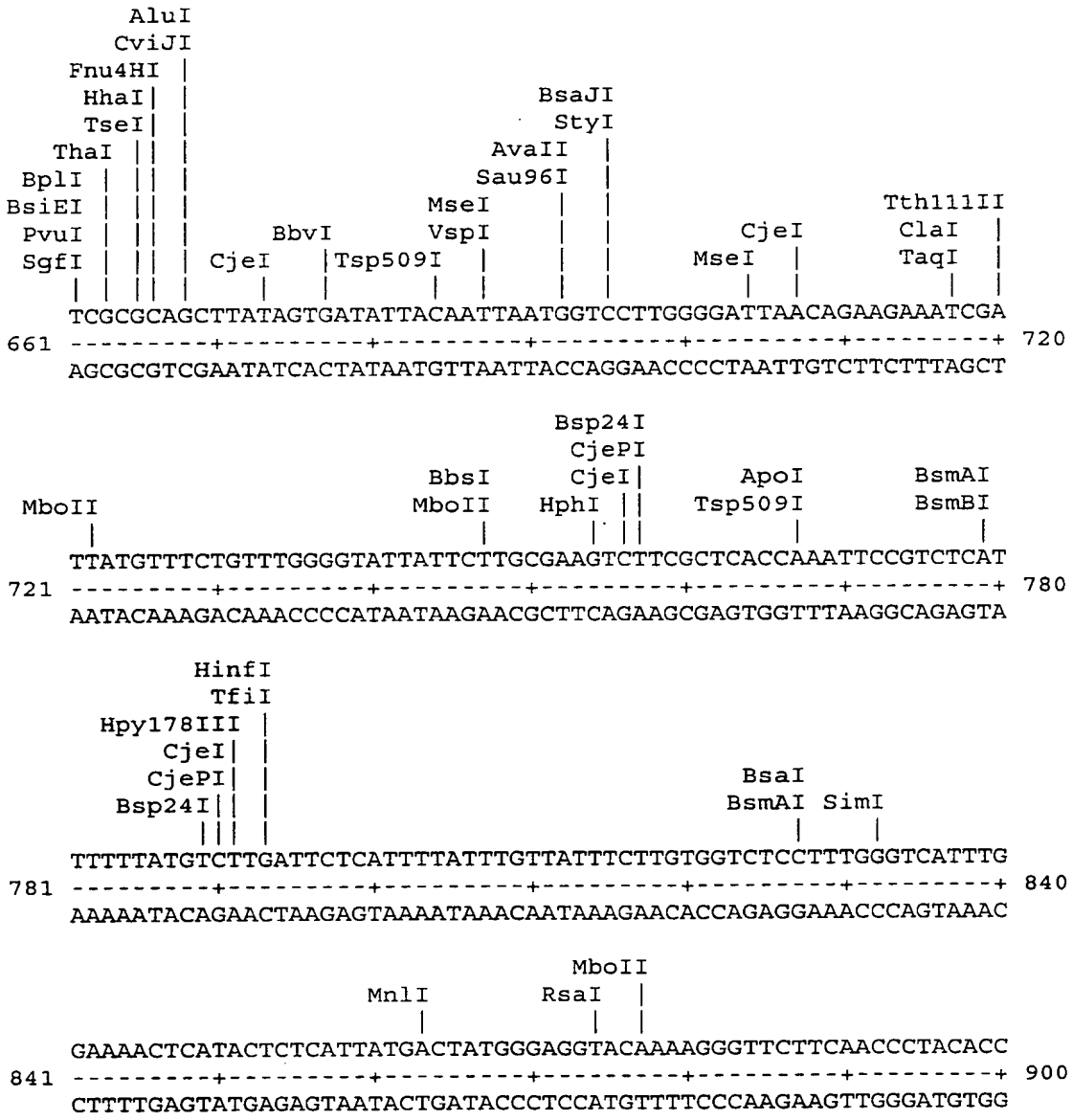
Fig. 8 (con't)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VspI
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CjePI
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BsmAI
SimI
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MnlI
RsaI
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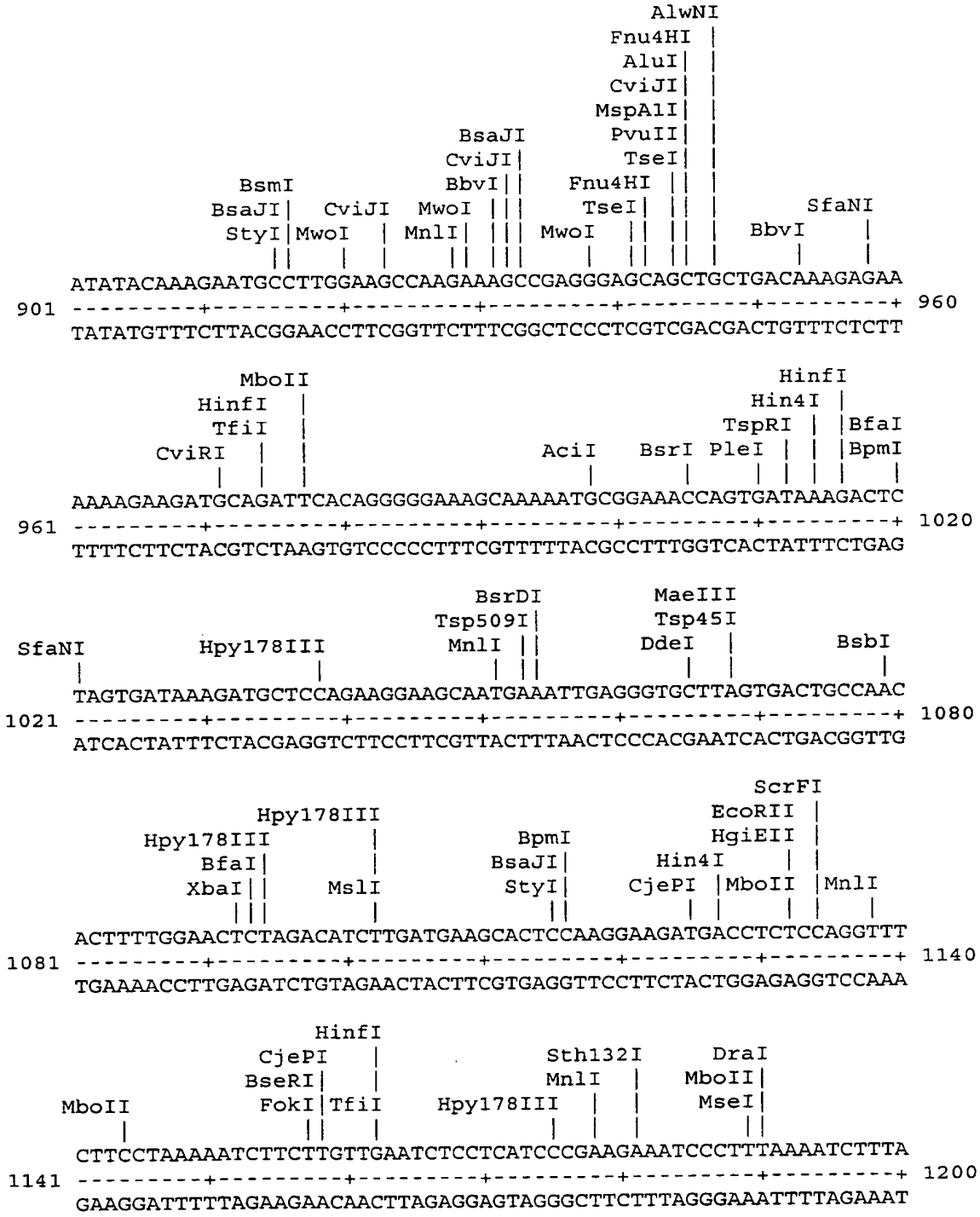
Fig. 8 (con't)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BsaJI
CviJI
MwoI
TseI
SfaNI
StyI
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Tsp509I
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ScrFI
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Hpy178III
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Hin4I
XbaI
MslI
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MnlI
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Figure 9: CPN100426

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                                              Met Thr Ile Arg Val
                                                1               5

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Pro Thr Gln Gly Asp Ile Trp Ile Glu Gly Glu Ala Pro Ala Leu Val
    55                  60                  65

ttc caa caa ccc gag tta ttt tcc cat atg aca gta tta gga aat tgc   355
Phe Gln Gln Pro Glu Leu Phe Ser His Met Thr Val Leu Gly Asn Cys
70                  75                  80                  85

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Thr His Pro Gln Ile His Ile Lys Gly Arg Ser Thr Glu Glu Ala Arg
                90                  95                  100

gaa aag gcg ttc gag ctt tta cat ttg ttg gat att gaa gag gtt gct   451
Glu Lys Ala Phe Glu Leu Leu His Leu Leu Asp Ile Glu Glu Val Ala
            105                 110                 115

aag aat tat cct gac cag ctc tct ggg gga caa aaa caa cgt gtg gct   499
Lys Asn Tyr Pro Asp Gln Leu Ser Gly Gly Gln Lys Gln Arg Val Ala
        120                 125                 130

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Ile Val Arg Ser Leu Cys Met Asp Lys His Thr Leu Leu Phe Asp Glu
    135                 140                 145

cct aca tcg gct tta gat cct ttt gct acg gca tcg ttc cga cat ctt   595
Pro Thr Ser Ala Leu Asp Pro Phe Ala Thr Ala Ser Phe Arg His Leu
150                 155                 160                 165

tta gaa aca ctt cga gac cag gaa ctg act gta ggg tta act act cat   643
Leu Glu Thr Leu Arg Asp Gln Glu Leu Thr Val Gly Leu Thr Thr His
                170                 175                 180

gac atg caa ttt gtt cat agt tgt ttg gat cgt atc tat ctt ata gat   691
Asp Met Gln Phe Val His Ser Cys Leu Asp Arg Ile Tyr Leu Ile Asp
            185                 190                 195
```

Fig. 9 (con't)

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Ser Gly His Pro Leu Ser Lys Tyr Ile His Ser Ala Gln
    215                 220                 225

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Figure 10 (RY-37)
Restriction enzyme analysis of CPN100426

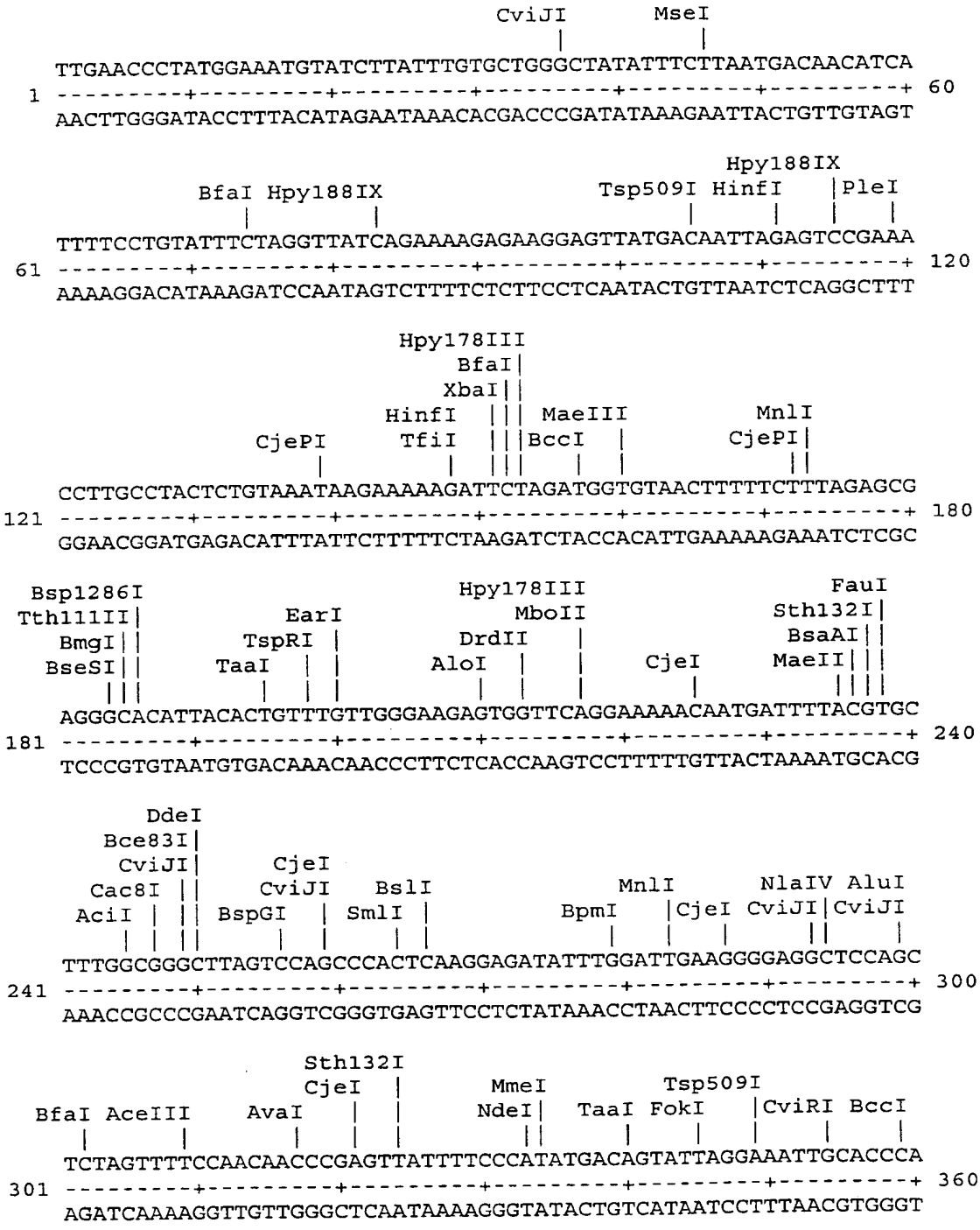
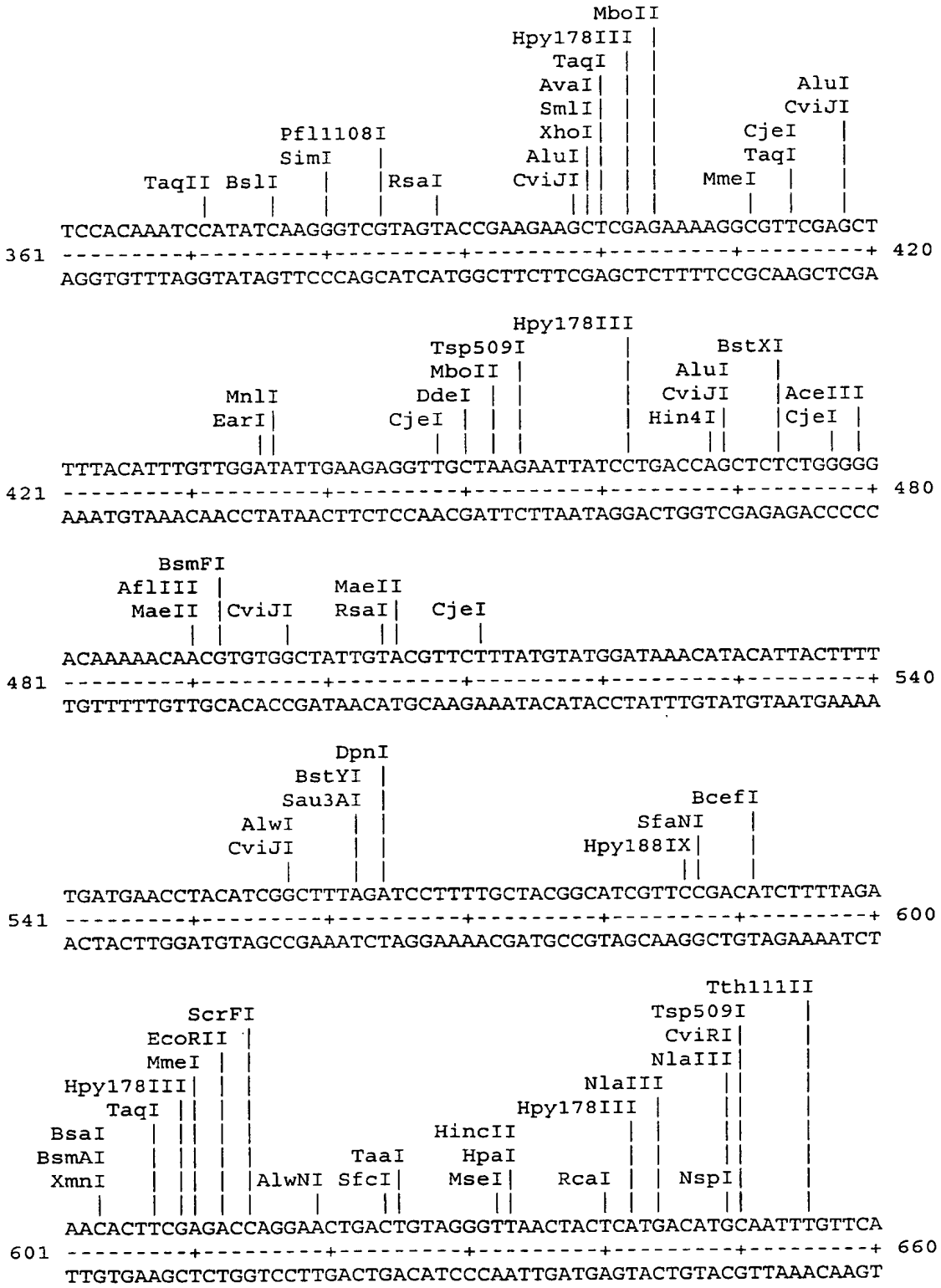


Fig. 10 (con't)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Pfl1108I
SimI
TaqII BslI
RsaI
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CjeI
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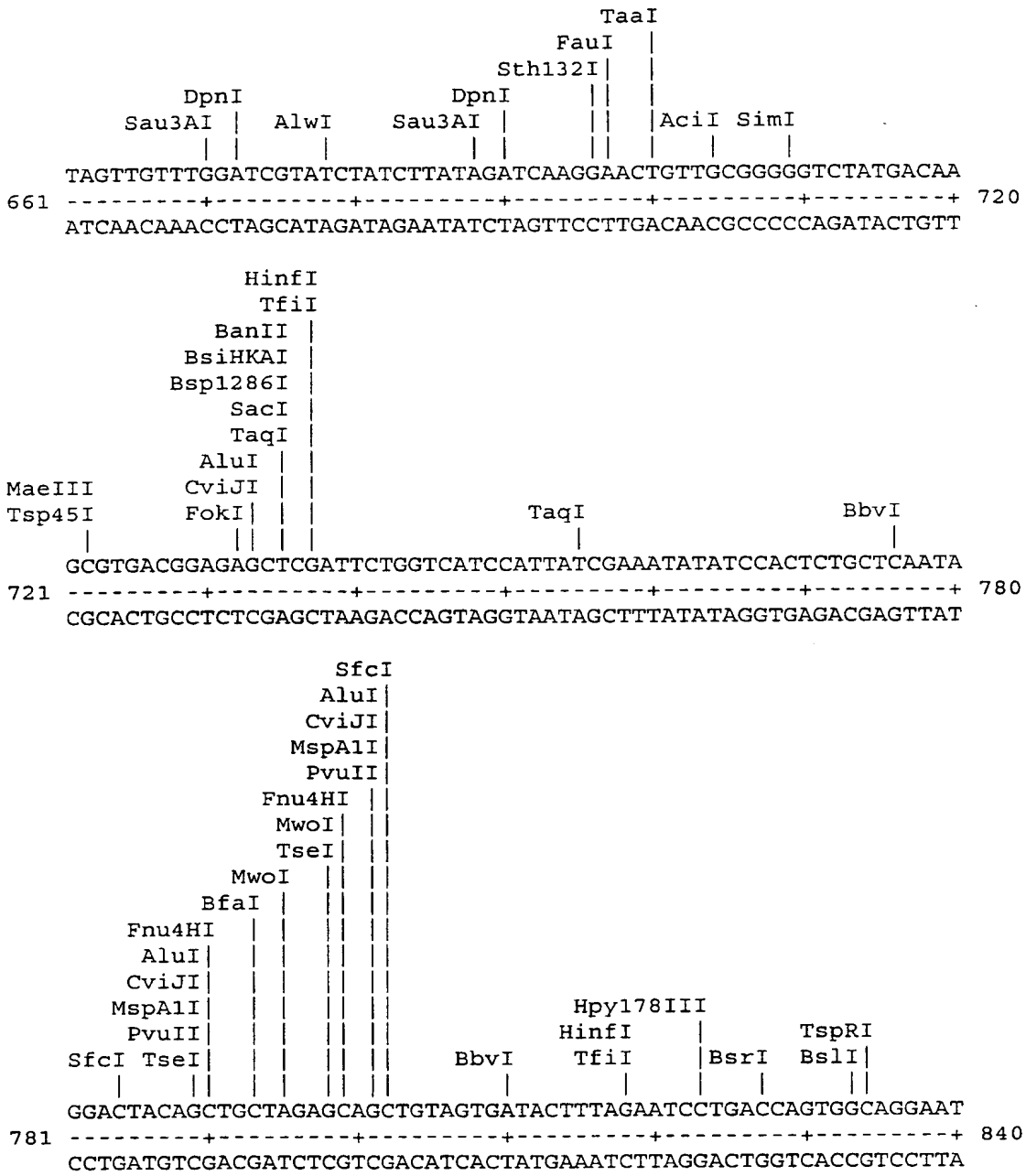
Fig. 10 (con't)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HinfI
TfiI
BanII
BsiHKAI
Bsp1286I
SacI
TaqI
AluI
MaeIII
CviJI
Tsp45I
FokI
TaqI
BbvI
GCGTGACGGAGAGCTCGATTCTGGTCATCCATTATCGAAATATATCCACTCTGCTCAATA
721
780
CGCACTGCCTCTCGAGCTAAGACCAGTAGGTAATAGCTTTATATAGGTGAGACGAGTTAT
SfcI
AluI
CviJI
MspA1I
PvuII
Fnu4HI
MwoI
TseI
MwoI
BfaI
Fnu4HI
AluI
CviJI
MspA1I
PvuII
SfcI
TseI
Hpy178III
HinfI
TspRI
BbvI
TfiI
BsrI
BslI
GGACTACAGCTGCTAGAGCAGCTGTAGTGATACTTTAGAATCCTGACCAGTGGCAGGAAT
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840
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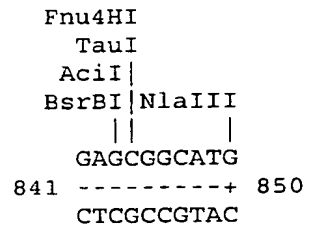
Fig. 10 (con't)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TauI
AciI
BsrBI
NlaIII
GAGCGGCATG
841
850
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Figure 11: CPN100508

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ttcctaataa cgtaagtaat aaacaatcaa aagtccgcat atg aaa aga cct ttt   115
                                            Met Lys Arg Pro Phe
                                              1               5

ttt acc tat cta tgc atc atc ttc tac gga tct tgt gca tcg tta tct   163
Phe Thr Tyr Leu Cys Ile Ile Phe Tyr Gly Ser Cys Ala Ser Leu Ser
                 10                  15                  20

tta cat gca gga ctc tct ttc cca gaa gta cgt gga gct acg gct gct   211
Leu His Ala Gly Leu Ser Phe Pro Glu Val Arg Gly Ala Thr Ala Ala
             25                  30                  35

gtt gtc cat gcc gac tct ggg aag gta ttc tat gat aaa gac ata gat   259
Val Val His Ala Asp Ser Gly Lys Val Phe Tyr Asp Lys Asp Ile Asp
Val Val His Ala Asp Ser Gly Lys Val Phe Tyr Asp Lys Asp Ile Asp
         40                  45                  50

gct gta atc tat cct gcc agc atg acg aaa atc gca act gcc ctc ttt   307
Ala Val Ile Tyr Pro Ala Ser Met Thr Lys Ile Ala Thr Ala Leu Phe
Ala Val Ile Tyr Pro Ala Ser Met Thr Lys Ile Ala Thr Ala Leu Phe
     55                  60                  65

atc cta aag cac tat ccc aca gtc ctc gat act ctc atc aaa gtc aaa   355
Ile Leu Lys His Tyr Pro Thr Val Leu Asp Thr Leu Ile Lys Val Lys
Ile Leu Lys His Tyr Pro Thr Val Leu Asp Thr Leu Ile Lys Val Lys
 70                  75                  80                  85

caa gat gcg atc gct tcc atc act ccg caa gca aaa aaa caa tca gga   403
Gln Asp Ala Ile Ala Ser Ile Thr Pro Gln Ala Lys Lys Gln Ser Gly
Gln Asp Ala Ile Ala Ser Ile Thr Pro Gln Ala Lys Lys Gln Ser Gly
                 90                  95                  100

tat cgt agt cct ccc cac tgg tta gaa act gat gga tct aca ata cag   451
Tyr Arg Ser Pro Pro His Trp Leu Glu Thr Asp Gly Ser Thr Ile Gln
Tyr Arg Ser Pro Pro His Trp Leu Glu Thr Asp Gly Ser Thr Ile Gln
             105                 110                 115

ctc cat ctt cga gaa gag ctt tta ggg tgg gac ctg ttc cac gcc tta   499
Leu His Leu Arg Glu Glu Leu Leu Gly Trp Asp Leu Phe His Ala Leu
Leu His Leu Arg Glu Glu Leu Leu Gly Trp Asp Leu Phe His Ala Leu
         120                 125                 130

ctg gtc tgt tct gct aat gat gct gcg aat gtc tta gct atg gca tgt   547
Leu Val Cys Ser Ala Asn Asp Ala Ala Asn Val Leu Ala Met Ala Cys
Leu Val Cys Ser Ala Asn Asp Ala Ala Asn Val Leu Ala Met Ala Cys
     135                 140                 145

tgc gga tct gta gag aag ttt atg gat aag ctg aac ttc ttc tta aaa   595
Cys Gly Ser Val Glu Lys Phe Met Asp Lys Leu Asn Phe Phe Leu Lys
Cys Gly Ser Val Glu Lys Phe Met Asp Lys Leu Asn Phe Phe Leu Lys
150                 155                 160                 165

gaa gaa atc ggc tgc act cat acc cat ttt aat aat ccc cat ggg tta   643
Glu Glu Ile Gly Cys Thr His Thr His Phe Asn Asn Pro His Gly Leu
Glu Glu Ile Gly Cys Thr His Thr His Phe Asn Asn Pro His Gly Leu
                 170                 175                 180
```

Fig. 11 (con't)

```
cat cat ccg aat cac tat act aca acc cgt gat ctt att agc atc atg   691
His His Pro Asn His Tyr Thr Thr Thr Arg Asp Leu Ile Ser Ile Met
His His Pro Asn His Tyr Thr Thr Thr Arg Asp Leu Ile Ser Ile Met
            185                 190                 195

cgt tgc gct ctg aaa gaa cct cca ttt cga ggg gtc atc tcc acg aca   739
Arg Cys Ala Leu Lys Glu Pro Pro Phe Arg Gly Val Ile Ser Thr Thr
Arg Cys Ala Leu Lys Glu Pro Pro Phe Arg Gly Val Ile Ser Thr Thr
        200                 205                 210

agc tat aaa ata ggg gct aca aac ctg cat ggc gaa cgg atc cta tcc   787
Ser Tyr Lys Ile Gly Ala Thr Asn Leu His Gly Glu Arg Ile Leu Ser
Ser Tyr Lys Ile Gly Ala Thr Asn Leu His Gly Glu Arg Ile Leu Ser
    215                 220                 225

cca aca aac aaa ttg ctt ctt cct ggg tct acc tac cac tat ccc cca   835
Pro Thr Asn Lys Leu Leu Leu Pro Gly Ser Thr Tyr His Tyr Pro Pro
Pro Thr Asn Lys Leu Leu Leu Pro Gly Ser Thr Tyr His Tyr Pro Pro
230                 235                 240                 245

gct tta gga ggg aaa aca ggg acc acc aag act gca ggg aaa aat cta   883
Ala Leu Gly Gly Lys Thr Gly Thr Thr Lys Thr Ala Gly Lys Asn Leu
Ala Leu Gly Gly Lys Thr Gly Thr Thr Lys Thr Ala Gly Lys Asn Leu
                250                 255                 260

att atg gct gct gaa aaa aat aac cgc ctc ttg gta acg atc gca acg   931
Ile Met Ala Ala Glu Lys Asn Asn Arg Leu Leu Val Thr Ile Ala Thr
Ile Met Ala Ala Glu Lys Asn Asn Arg Leu Leu Val Thr Ile Ala Thr
            265                 270                 275

ggc tat tcg ggt cct gtg agt gat ctc tac caa gat gtc att gct cta   979
Gly Tyr Ser Gly Pro Val Ser Asp Leu Tyr Gln Asp Val Ile Ala Leu
Gly Tyr Ser Gly Pro
        280                 285                 290

tgt gaa acg gta ttt aac gag ccg cta tta aga aaa gag ctc gtc ccc   1027
Cys Glu Thr Val Phe Asn Glu Pro Leu Leu Arg Lys Glu Leu Val Pro
    295                 300                 305

ccc tcc gac tgt ctc caa tta gaa ata gcg aat ctt ggg aag ctt tct   1075
Pro Ser Asp Cys Leu Gln Leu Glu Ile Ala Asn Leu Gly Lys Leu Ser
310                 315                 320                 325

tgc cct ctt cct gag gga ctc tac tat gac ttc tat gcc tcc gaa gat   1123
Cys Pro Leu Pro Glu Gly Leu Tyr Tyr Asp Phe Tyr Ala Ser Glu Asp
                330                 335                 340

cgc gaa cct ctt tct gta tct ttt att gca cat gcg gac gcc ttc cct   1171
Arg Glu Pro Leu Ser Val Ser Phe Ile Ala His Ala Asp Ala Phe Pro
            345                 350                 355

att gaa caa gga gat ctt ctt ggt cat tgg gtt ttt tat gac gat gaa   1219
Ile Glu Gln Gly Asp Leu Leu Gly His Trp Val Phe Tyr Asp Asp Glu
        360                 365                 370
```

Fig. 11 (con't)

```
ggc aag aaa att tct tcc cag cct ttc tat gcc cct tgt cgt ttt gag   1267
Gly Lys Lys Ile Ser Ser Gln Pro Phe Tyr Ala Pro Cys Arg Phe Glu
    375                 380                 385

cgc act atc aag cct tgg aaa ctc tat atg aaa cgt gtc ttc aca tcg   1315
Arg Thr Ile Lys Pro Trp Lys Leu Tyr Met Lys Arg Val Phe Thr Ser
390                 395                 400                 405

tat aga acc tat atg tct ata acc atg ctg ctc atg tat ttt cgc atc   1363
Tyr Arg Thr Tyr Met Ser Ile Thr Met Leu Leu Met Tyr Phe Arg Ile
                410                 415                 420

cgc aag cac cgc aag tat aaa aat tta aaa cac tat tct aaa atc       1408
Arg Lys His Arg Lys Tyr Lys Asn Leu Lys His Tyr Ser Lys Ile
            425                 430                 435

taacttttttc ttttaattta taaaaaacca aaggtttatg taagatttgc gcttttcaat 1468

ccaacaagaa tcccttgtgc gcacattact tt                               1500
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Figure 12 (RY-39)

Restriction enzyme analysis of CPN100508

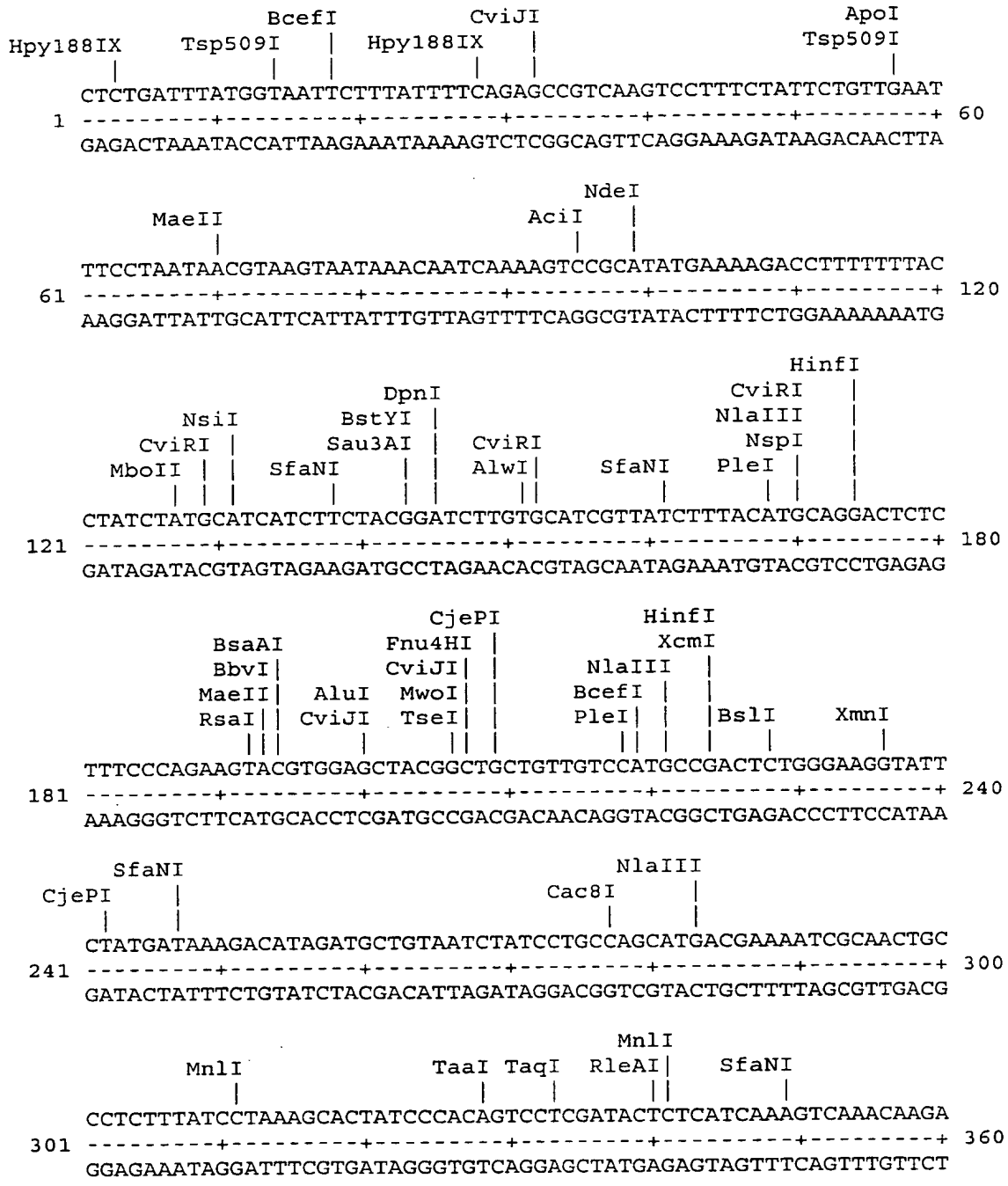
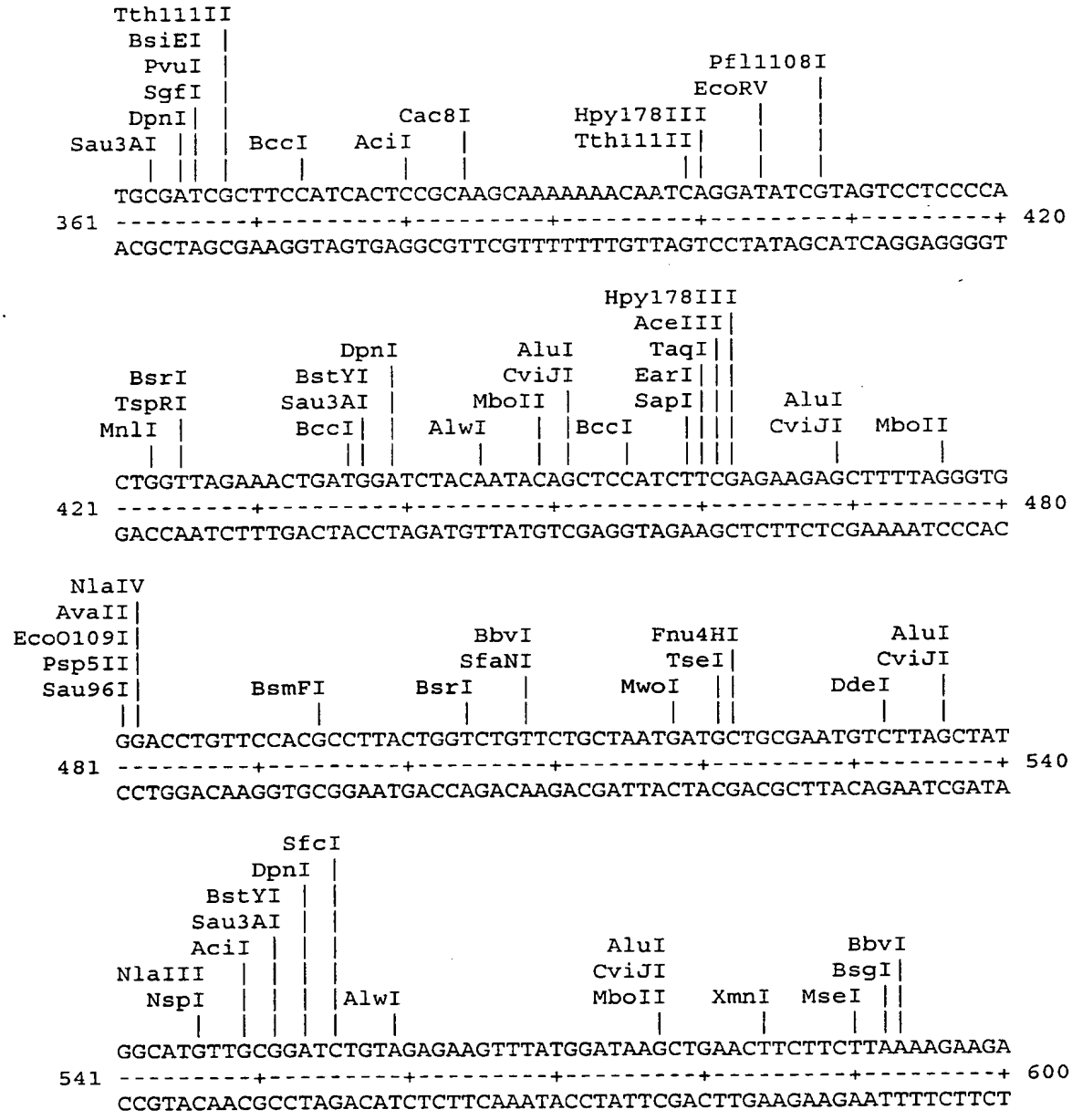


Fig. 12 (con't)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Tth111II
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361
ACGCTAGCGAAGGTAGTGAGGCGTTCGTTTTTTTGTTAGTCCTATAGCATCAGGAGGGGT
420
Hpy178III
AceIII
DpnI
AluI
TaqI
BsrI
BstYI
CviJI
EarI
TspRI
Sau3AI
MboII
SapI
AluI
MnlI
BccI
AlwI
BccI
CviJI
MboII
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AvaII
Eco0109I
Psp5II
Sau96I
BbvI
SfaNI
Fnu4HI
TseI
AluI
CviJI
BsmFI
BsrI
MwoI
DdeI
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481
CCTGGACAAGGTGCGGAATGACCAGACAAGACGATTACTACGACGCTTACAGAATCGATA
540
SfcI
DpnI
BstYI
Sau3AI
AciI
NlaIII
NspI
AlwI
AluI
CviJI
MboII
XmnI
BbvI
BsgI
MseI
GGCATGTTGCGGATCTGTAGAGAAGTTTATGGATAAGCTGAACTTCTTCTTAAAAGAAGA
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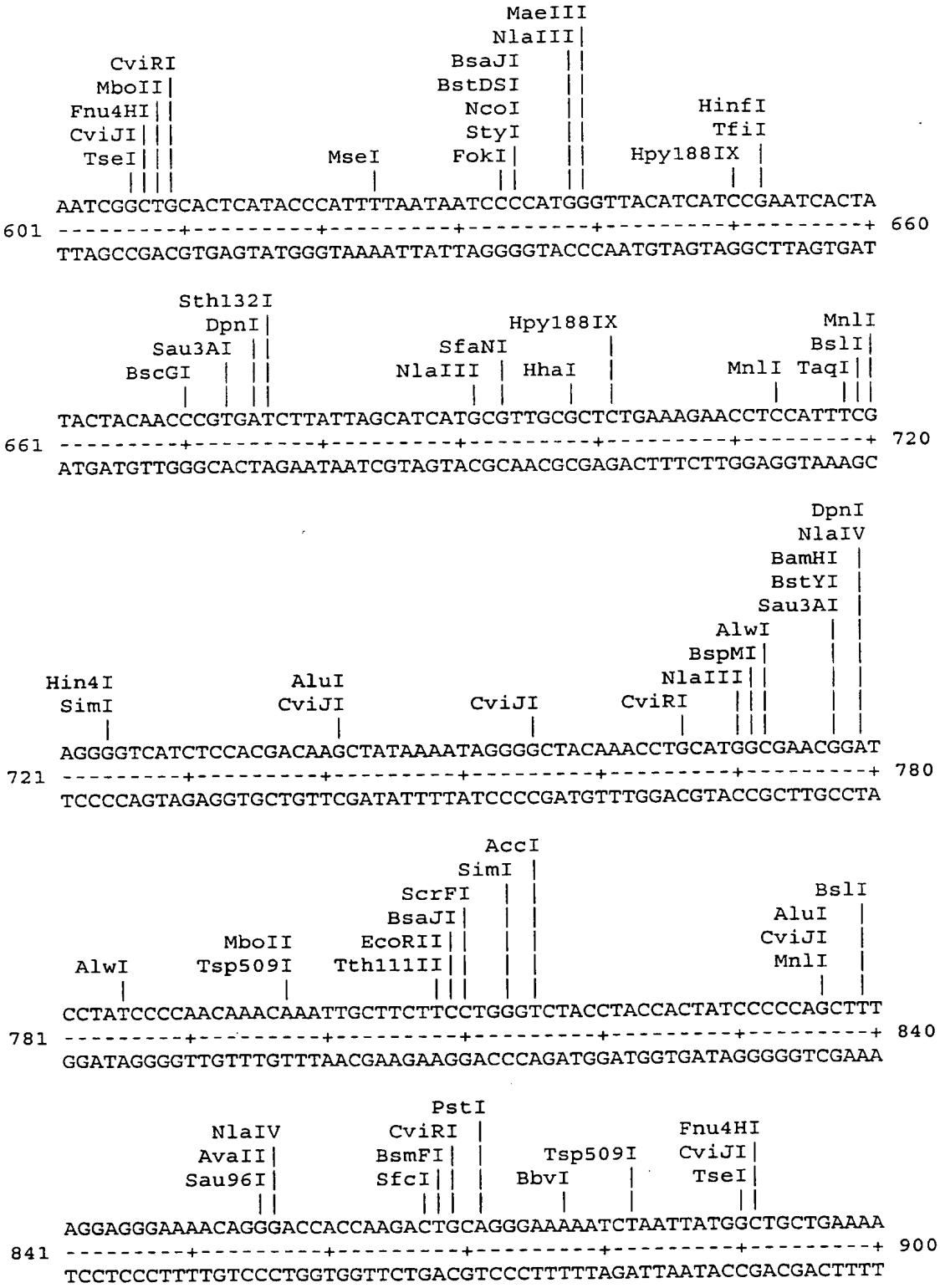
600

Fig. 12 (con't)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BsaJI
BstDSI
NcoI
StyI
FokI
MseI
HinfI
TfiI
Hpy188IX
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TTAGCCGACGTGAGTATGGGTAAAATTATTAGGGGTACCCAATGTAGTAGGCTTAGTGAT
Sth132I
DpnI
Sau3AI
BscGI
Hpy188IX
SfaNI
NlaIII
HhaI
MnlI
BslI
MnlI
TaqI
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661 720
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DpnI
NlaIV
BamHI
BstYI
Sau3AI
AlwI
BspMI
NlaIII
Hin4I
SimI
AluI
CviJI
CviJI
CviRI
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721 780
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AccI
SimI
ScrFI
BsaJI
EcoRII
Tth111II
MboII
Tsp509I
AlwI
BslI
AluI
CviJI
MnlI
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PstI
NlaIV
AvaII
Sau96I
CviRI
BsmFI
SfcI
Tsp509I
BbvI
Fnu4HI
CviJI
TseI
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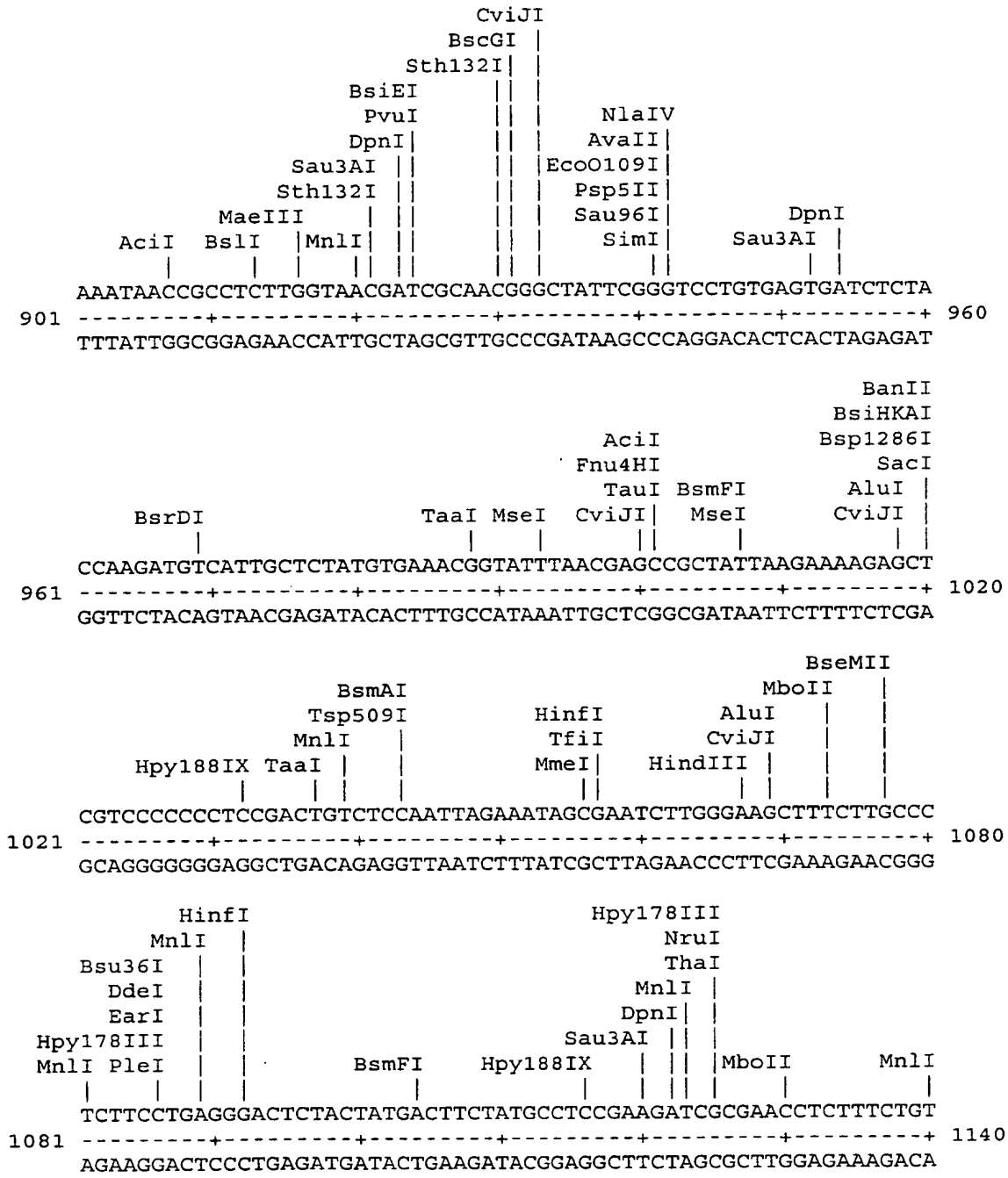
Fig. 12 (con't)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BsiEI
PvuI
DpnI
Sau3AI
Sth132I
MaeIII
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NlaIV
AvaII
EcoO109I
Psp5II
Sau96I
SimI
DpnI
Sau3AI
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901 960
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BsiHKAI
Bsp1286I
SacI
AluI
CviJI
AciI
Fnu4HI
TauI
BsmFI
MseI
BsrDI
TaaI MseI CviJI
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961 1020
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BseMII
MboII
BsmAI
Tsp509I
MnlI
AluI
CviJI
HinfI
TfiI
MmeI
HindIII
Hpy188IX TaaI
CGTCCCCCCCTCCGACTGTCTCCAATTAGAAATAGCGAATCTTGGGAAGCTTTCTTGCCC
1021 1080
GCAGGGGGGGAGGCTGACAGAGGTTAATCTTTATCGCTTAGAACCCTTCGAAAGAACGGG
HinfI
MnlI
Bsu36I
DdeI
EarI
Hpy178III
MnlI PleI
Hpy178III
NruI
ThaI
MnlI
DpnI
Sau3AI
BsmFI
Hpy188IX
MboII
MnlI
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1081 1140
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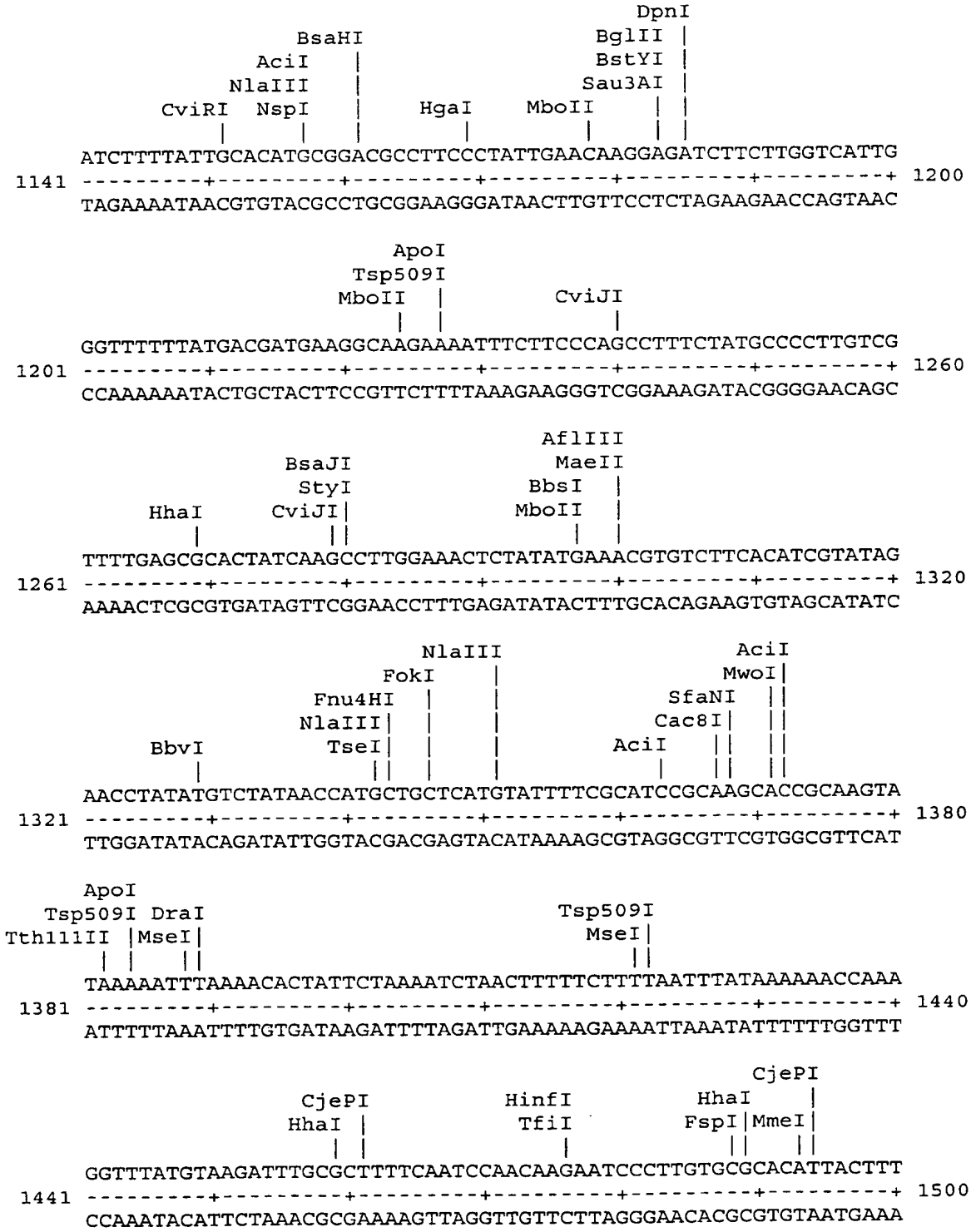
Fig. 12 (con't)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BstYI
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HgaI
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Tsp509I
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CviJI
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BsaJI
MaeII
StyI
BbsI
HhaI
CviJI
MboII
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Fnu4HI
SfaNI
NlaIII
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TseI
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DraI
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CjePI
CjePI
HinfI
HhaI
HhaI
TfiI
FspI
MmeI
GGTTTATGTAAGATTTGCGCTTTTCAATCCAACAAGAATCCCTTGTGCGCACATTACTTT
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CCAAATACATTCTAAACGCGAAAAGTTAGGTTGTTCTTAGGGAACACGCGTGTAATGAAA

Figure 13: CPN100515 -

```
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tcgcaataat aacttgccta aacgatcttg taaacgactt atg gct tct aat ccc   115
                                            Met Ala Ser Asn Pro
                                              1               5

att tta cag ata gag gat cta tcc ata acc ttg gca aaa caa cgc caa   163
Ile Leu Gln Ile Glu Asp Leu Ser Ile Thr Leu Ala Lys Gln Arg Gln
Ile Leu Gln Ile Glu Asp Leu Ser Ile Thr Leu Ala Lys Gln Arg Gln
                  10                  15                  20

cag tac ccc atc gtc caa tct tta tcg ttt act atc aat gaa gga caa   211
Gln Tyr Pro Ile Val Gln Ser Leu Ser Phe Thr Ile Asn Glu Gly Gln
Gln Tyr Pro Ile Val Gln Ser Leu Ser Phe Thr Ile Asn Glu Gly Gln
             25                  30                  35

acc tta gca atc att gga gaa tca gga tca gga aaa tct gtc tct gcg   259
Thr Leu Ala Ile Ile Gly Glu Ser Gly Ser Gly Lys Ser Val Ser Ala
Thr Leu Ala Ile Ile Gly Glu Ser Gly Ser Gly Lys Ser Val Ser Ala
         40                  45                  50

cat gca atc ctt cga tta ctt cct tgc ccc cca ttt tct gtt tct ggc   307
His Ala Ile Leu Arg Leu Leu Pro Cys Pro Pro Phe Ser Val Ser Gly
His Ala Ile Leu Arg Leu Leu Pro Cys Pro Pro Phe Ser Val Ser Gly
     55                  60                  65

cag gtc aac ttc caa ggc cac aac tta ctt acg gct tcg cgc tct ata   355
Gln Val Asn Phe Gln Gly His Asn Leu Leu Thr Ala Ser Arg Ser Ile
Gln Val Asn Phe Gln Gly His Asn Leu Leu Thr Ala Ser Arg Ser Ile
 70                  75                  80                  85

caa aaa aag att ata ggg aca gaa att tct atg atc ttt caa aac ccg   403
Gln Lys Lys Ile Ile Gly Thr Glu Ile Ser Met Ile Phe Gln Asn Pro
Gln Lys Lys Ile Ile Gly Thr Glu Ile Ser Met Ile Phe Gln Asn Pro
                  90                  95                 100

caa gca tct cta aac ccc gtg ttt act att gaa cag cag ttt cga gaa   451
Gln Ala Ser Leu Asn Pro Val Phe Thr Ile Glu Gln Gln Phe Arg Glu
Gln Ala Ser Leu Asn Pro Val Phe Thr Ile Glu Gln Gln Phe Arg Glu
             105                 110                 115

att att cat acc cac cta gcc tta act gca gaa gtt gct aaa gaa aag   499
Ile Ile His Thr His Leu Ala Leu Thr Ala Glu Val Ala Lys Glu Lys
Ile Ile His Thr His Leu Ala Leu Thr Ala Glu Val Ala Lys Glu Lys
         120                 125                 130

atg tta tac gct ctt gaa gaa aca ggg ttt cat gat ccc agg ctg tgc   547
Met Leu Tyr Ala Leu Glu Glu Thr Gly Phe His Asp Pro Arg Leu Cys
Met Leu Tyr Ala Leu Glu Glu Thr Gly Phe His Asp Pro Arg Leu Cys
     135                 140                 145

ttg aat ctc tac ccc cac caa ctc tct gga ggg atg ctt caa aga att   595
Leu Asn Leu Tyr Pro His Gln Leu Ser Gly Gly Met Leu Gln Arg Ile
Leu Asn Leu Tyr Pro His Gln Leu Ser Gly Gly Met Leu Gln Arg Ile
150                 155                 160                 165
```

Fig. 13 (con't)

```
tgc att gcc atg gcg ctc ctc tgt tct cct aaa ctt ctt att gct gat   643
Cys Ile Ala Met Ala Leu Leu Cys Ser Pro Lys Leu Leu Ile Ala Asp
Cys Ile Ala Met Ala Leu Leu Cys Ser Pro Lys Leu Leu Ile Ala Asp
                170                 175                 180

gaa cct acg act gct tta gat gtt tct gtt cag tat cag att cta caa   691
Glu Pro Thr Thr Ala Leu Asp Val Ser Val Gln Tyr Gln Ile Leu Gln
Glu Pro Thr Thr Ala Leu Asp Val Ser Val Gln Tyr Gln Ile Leu Gln
            185                 190                 195

tta cta aaa aca cta cag aaa aaa acg gga atg agc ctt ctt att att   739
Leu Leu Lys Thr Leu Gln Lys Lys Thr Gly Met Ser Leu Leu Ile Ile
Leu Leu Lys Thr Leu Gln Lys Lys Thr Gly Met Ser Leu Leu Ile Ile
        200                 205                 210

acc cat aat atg gga gtc gtt gca gaa act gct gat gac gtg ctc gtg   787
Thr His Asn Met Gly Val Val Ala Glu Thr Ala Asp Asp Val Leu Val
Thr His Asn Met Gly Val Val Ala Glu Thr Ala Asp Asp Val Leu Val
    215                 220                 225

ctc tat gca gga cgc atg gta gaa tgt gcc cct gcg gtt caa atg ttc   835
Leu Tyr Ala Gly Arg Met Val Glu Cys Ala Pro Ala Val Gln Met Phe
Leu Tyr Ala Gly Arg Met Val Glu Cys Ala Pro Ala Val Gln Met Phe
230                 235                 240                 245

cat aat cct tct cat ccc tat acc cga gat ctt tta gca tcc aga ccc   883
His Asn Pro Ser His Pro Tyr Thr Arg Asp Leu Leu Ala Ser Arg Pro
His Asn Pro Ser His Pro Tyr Thr Arg Asp Leu Leu Ala Ser Arg Pro
                250                 255                 260

tct cta caa ccg caa caa cta ggt tcc ttc aac ccc att cca gga cag   931
Ser Leu Gln Pro Gln Gln Leu Gly Ser Phe Asn Pro Ile Pro Gly Gln
Ser Leu Gln Pro Gln Gln Leu Gly Ser Phe Asn Pro Ile Pro Gly Gln
            265                 270                 275

ccc cca cac tac acg gcc ttt ccc tcg gga tgt cgc tat cac cct aga   979
Pro Pro His Tyr Thr Ala Phe Pro Ser Gly Cys Arg Tyr His Pro Arg
Pro Pro His Tyr Thr Ala Phe Pro Ser Gly Cys Arg Tyr His Pro Arg
        280                 285                 290

tgc tca aaa att tta aat cga tgt tct gcg gaa gct cca gaa atc tat   1027
Cys Ser Lys Ile Leu Asn Arg Cys Ser Ala Glu Ala Pro Glu Ile Tyr
Cys Ser Lys Ile Leu Asn Arg Cys Ser Ala Glu Ala Pro Glu Ile Tyr
    295                 300                 305

ccg gta cgc gaa ggt cac aaa gta agg gtt ggc tgt atg acg act aat   1075
Pro Val Arg Glu Gly His Lys Val Arg Val Gly Cys Met Thr Thr Asn
Pro Val Arg Glu Gly His Lys Val Arg Val Gly Cys Met Thr Thr Asn
310                 315                 320                 325

ttt ccc caa cct tta att caa gca acc tca tta aca aag cac tat tac   1123
Phe Pro Gln Pro Leu Ile Gln Ala Thr Ser Leu Thr Lys His Tyr Tyr
Phe Pro Gln Pro Leu Ile Gln Ala Thr Ser Leu Thr Lys His Tyr Tyr
                330                 335                 340
```

Fig. 13 (con't)

```
aag cgt tcc ttt tgg ttt cag gga aag aca att gcc agt cgt cct gtt   1171
Lys Arg Ser Phe Trp Phe Gln Gly Lys Thr Ile Ala Ser Arg Pro Val
Lys Arg Ser Phe Trp Phe Gln Gly Lys Thr Ile Ala Ser Arg Pro Val
            345                 350                 355

gac gac gtc tct ttt tca cta tac tcc aga cgt gct gtc gga ctt att   1219
Asp Asp Val Ser Phe Ser Leu Tyr Ser Arg Arg Ala Val Gly Leu Ile
Asp Asp Val Ser Phe Ser Leu Tyr Ser Arg Arg Ala Val Gly Leu Ile
        360                 365                 370

gga gaa tct gga tca ggg aaa agt acc ctg gcg tta gct ctc gca ggt   1267
Gly Glu Ser Gly Ser Gly Lys Ser Thr Leu Ala Leu Ala Leu Ala Gly
Gly Glu Ser Gly Ser Gly Lys Ser Thr Leu Ala Leu Ala Leu Ala Gly
    375                 380                 385

ctc cta cct ctc acc tct ggg ttc tta act ttt aac ggc acc cca atc   1315
Leu Leu Pro Leu Thr Ser Gly Phe Leu Thr Phe Asn Gly Thr Pro Ile
Leu Leu Pro Leu Thr Ser Gly Phe Leu Thr Phe Asn Gly Thr Pro Ile
390                 395                 400                 405

aag ttg cat tct aaa cac gga cgc cat caa tta cga tct caa gta cgg   1363
Lys Leu His Ser Lys His Gly Arg His Gln Leu Arg Ser Gln Val Arg
Lys Leu His Ser Lys His Gly Arg His Gln Leu Arg Ser Gln Val Arg
                410                 415                 420

ttg gtc ttt caa aat cca caa gct tca tta aac ccg cga aaa act atc   1411
Leu Val Phe Gln Asn Pro Gln Ala Ser Leu Asn Pro Arg Lys Thr Ile
Leu Val Phe Gln Asn Pro Gln Ala Ser Leu Asn Pro Arg Lys Thr Ile
            425                 430                 435

cta gat agt tta ggc cac tct ctg ctt tac cat aaa ctc gtc cca aaa   1459
Leu Asp Ser Leu Gly His Ser Leu Leu Tyr His Lys Leu Val Pro Lys
Leu Asp Ser Leu Gly His Ser Leu Leu Tyr His Lys Leu Val Pro Lys
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gaa aaa gta cta gca acg gta agg gaa tat tta gaa ttg gta ggg tta   1507
Glu Lys Val Leu Ala Thr Val Arg Glu Tyr Leu Glu Leu Val Gly Leu
Glu Lys Val Leu Ala Thr Val Arg Glu Tyr Leu Glu Leu Val Gly Leu
    455                 460                 465

tct gag gag tat ttt tat cgt tat cct cac cag ctt tct gga gga caa   1555
Ser Glu Glu Tyr Phe Tyr Arg Tyr Pro His Gln Leu Ser Gly Gly Gln
Ser Glu Glu Tyr Phe Tyr Arg Tyr Pro His Gln Leu Ser Gly Gly Gln
470                 475                 480                 485

caa caa cga gtc tct ata gcg aga gcc cta tta gga gtc cct cag tta   1603
Gln Gln Arg Val Ser Ile Ala Arg Ala Leu Leu Gly Val Pro Gln Leu
Gln Gln Arg Val Ser Ile Ala Arg Ala Leu Leu Gly Val Pro Gln Leu
                490                 495                 500

att att tgt gac gaa att gtt tct gct cta gat tta tct att caa gca   1651
Ile Ile Cys Asp Glu Ile Val Ser Ala Leu Asp Leu Ser Ile Gln Ala
Ile Ile Cys Asp Glu Ile Val Ser Ala Leu Asp Leu Ser Ile Gln Ala
            505                 510                 515

caa att ctg aat atg ctt gcc gag ctg caa aaa aaa ctc agc ctc aca   1699
Gln Ile Leu Asn Met Leu Ala Glu Leu Gln Lys Lys Leu Ser Leu Thr
Gln Ile Leu Asn Met Leu Ala Glu Leu Gln Lys Lys Leu Ser Leu Thr
        520                 525                 530
```

Fig. 13 (con't)

```
tat ctc ttc att tcg cat gat ctt gcc gtt gta cgc tcg ttc tgc aca   1747
Tyr Leu Phe Ile Ser His Asp Leu Ala Val Val Arg Ser Phe Cys Thr
Tyr Leu Phe Ile Ser His Asp Leu Ala Val Val Arg Ser Phe Cys Thr
    535                 540                 545

gag gta ttc att atg tat aag ggg caa att gta gaa aaa gga aat aca   1795
Glu Val Phe Ile Met Tyr Lys Gly Gln Ile Val Glu Lys Gly Asn Thr
Glu Val Phe Ile Met Tyr Lys Gly Gln Ile Val Glu Lys Gly Asn Thr
550                 555                 560                 565

aaa cgc att ttt tct gat cca caa cat cct tat acg cgc atg ttg tta   1843
Lys Arg Ile Phe Ser Asp Pro Gln His Pro Tyr Thr Arg Met Leu Leu
Lys Arg Ile Phe Ser Asp Pro Gln His Pro Tyr Thr Arg Met Leu Leu
                570                 575                 580

aat gcc caa ctt cca gag act cct gat caa agg caa tct aaa cct ata   1891
Asn Ala Gln Leu Pro Glu Thr Pro Asp Gln Arg Gln Ser Lys Pro Ile
Asn Ala Gln Leu Pro Glu Thr Pro Asp Gln Arg Gln
            585                 590                 595

ttc caa gaa tat cac aaa gat tct gaa gaa tct tgc tct aca gga tgc   1939
Phe Gln Glu Tyr His Lys Asp Ser Glu Glu Ser Cys Ser Thr Gly Cys
        600                 605                 610

tac ttt tac aat cgt tgt cca caa aaa caa gaa gct tgc aag tca gag   1987
Tyr Phe Tyr Asn Arg Cys Pro Gln Lys Gln Glu Ala Cys Lys Ser Glu
    615                 620                 625

atc atc cca aat caa gga gac gcg cac cat aca tac cgt tgt atc cat   2035
Ile Ile Pro Asn Gln Gly Asp Ala His His Thr Tyr Arg Cys Ile His
630                 635                 640                 645

tgattcgtcc tctacgctat tcttaagcta ccattaagga atcccaaggg agaggtctgc 2095

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Figure 14 (RY-40)

Restriction enzyme analysis of CPN 100515

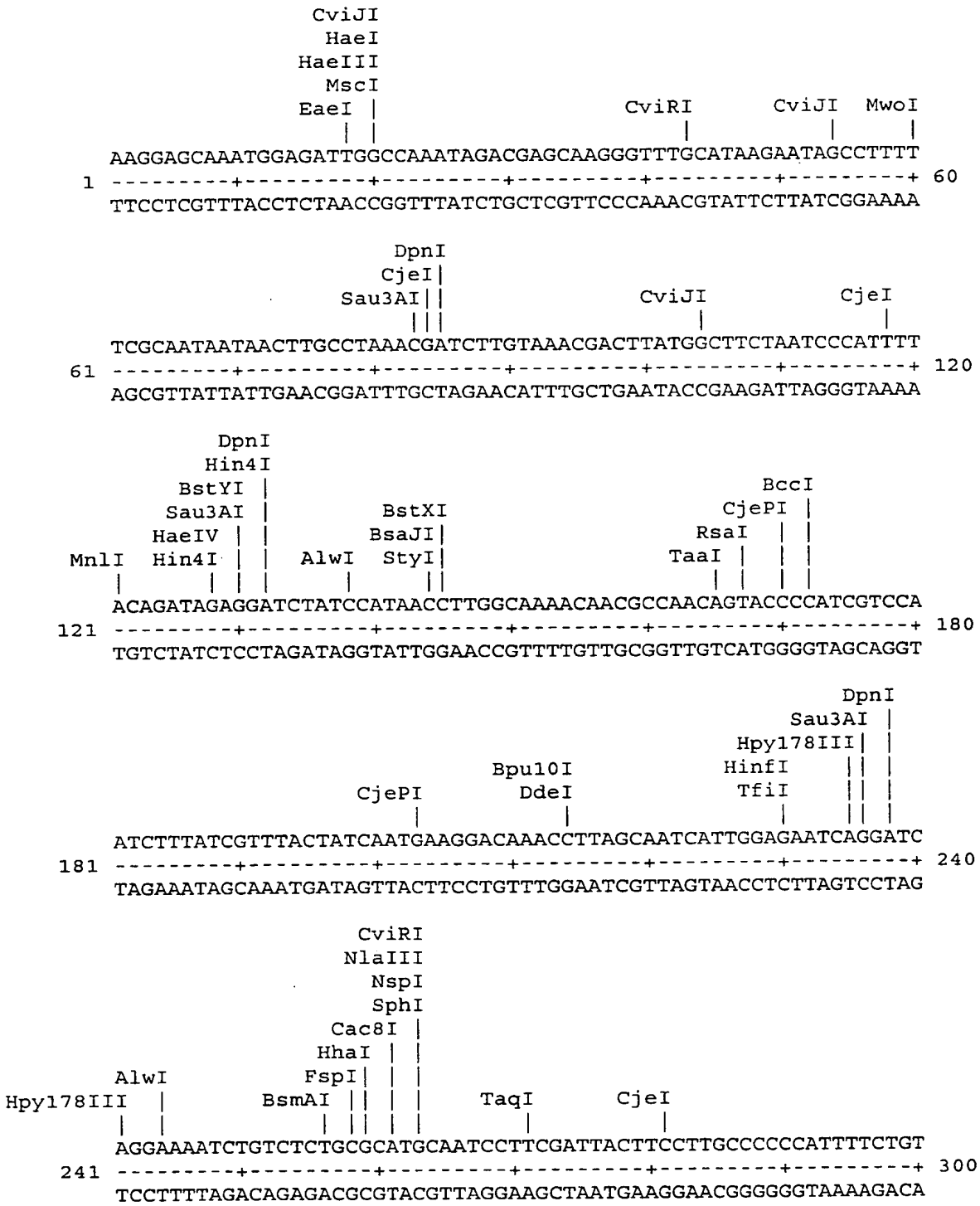
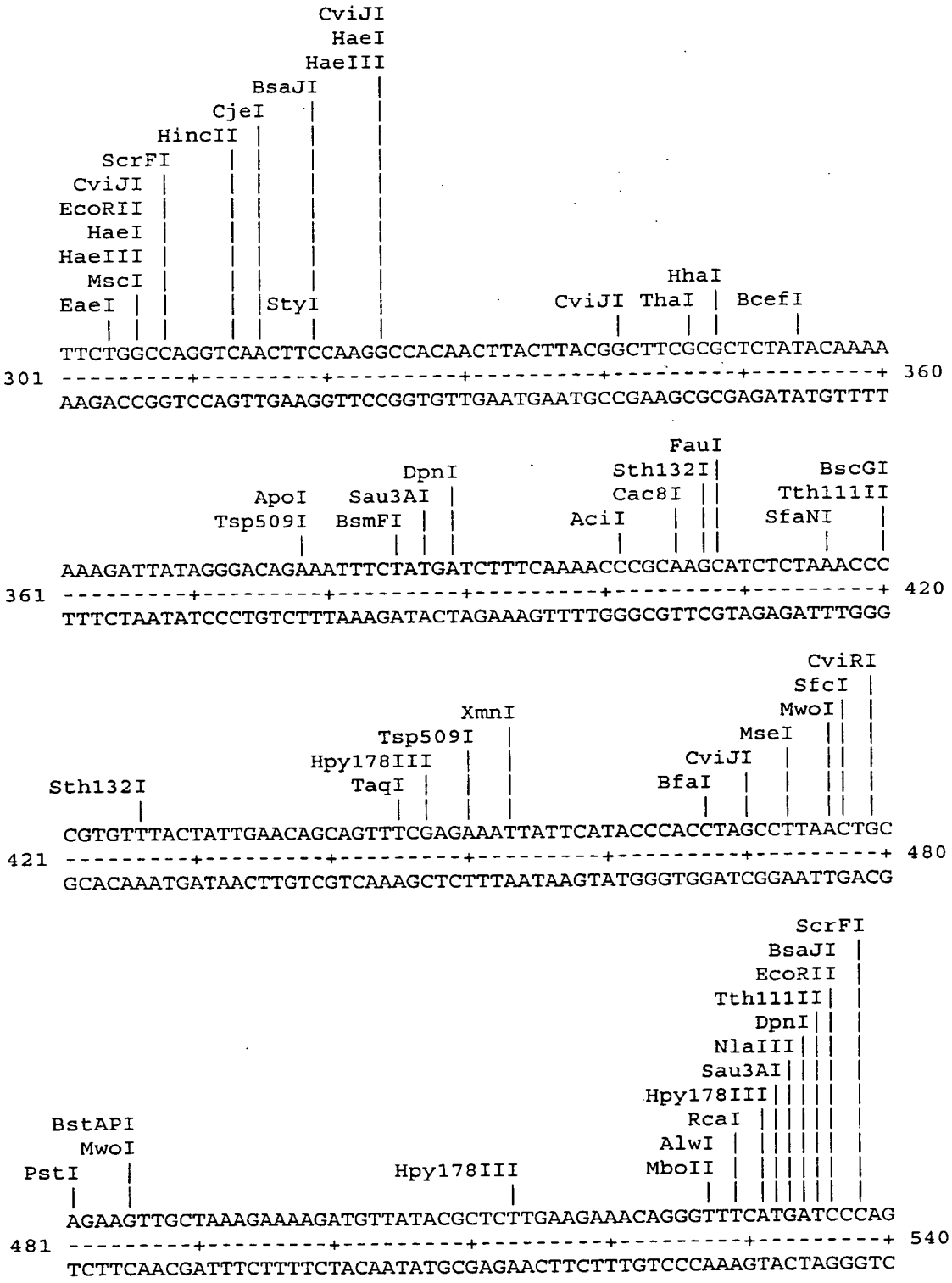


Fig. 14 (con't)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BcefI
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Tth111II
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Tth111II
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Fig. 14 (con't)

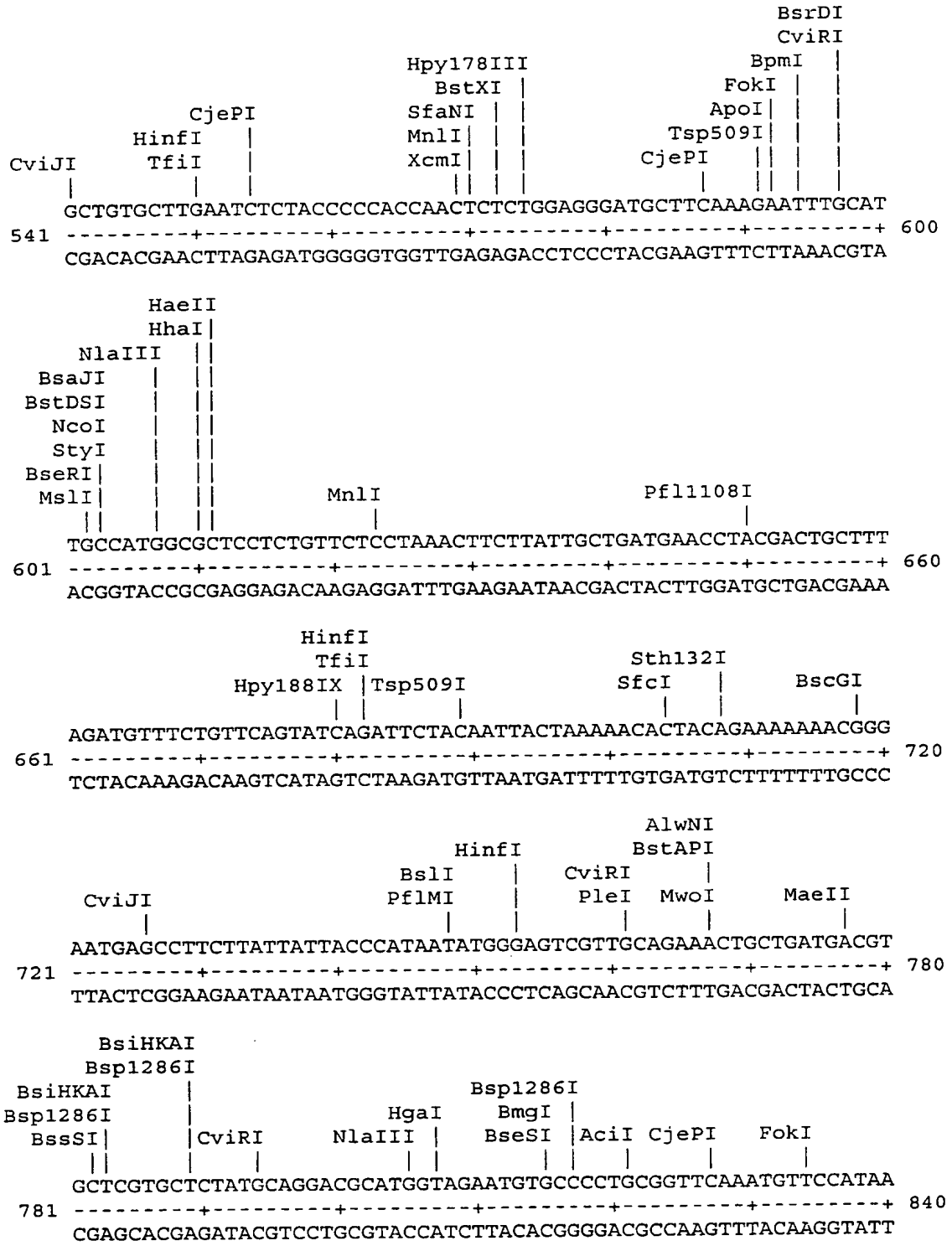
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Fig. 14 (con't)

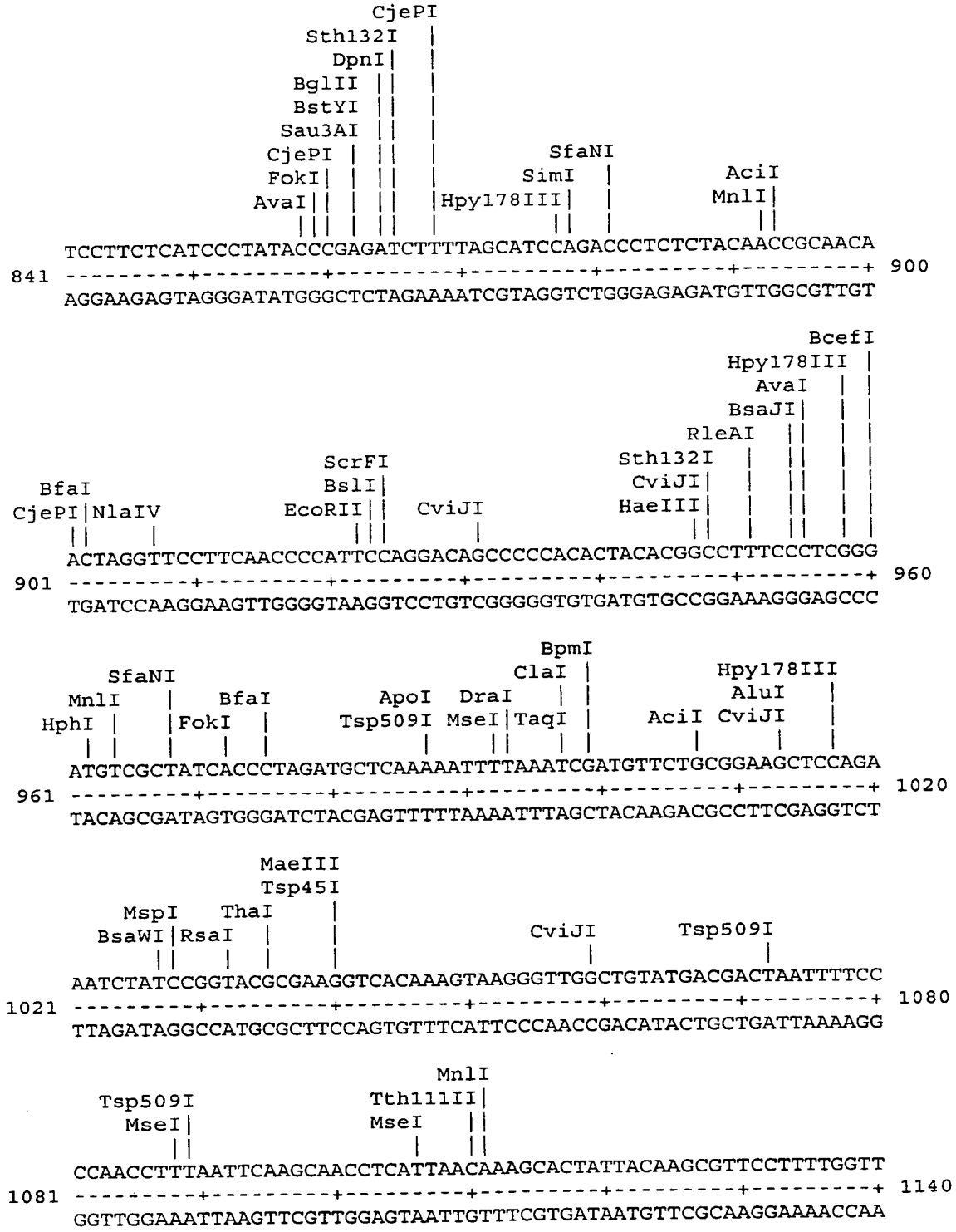
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Fig. 14 (con't)

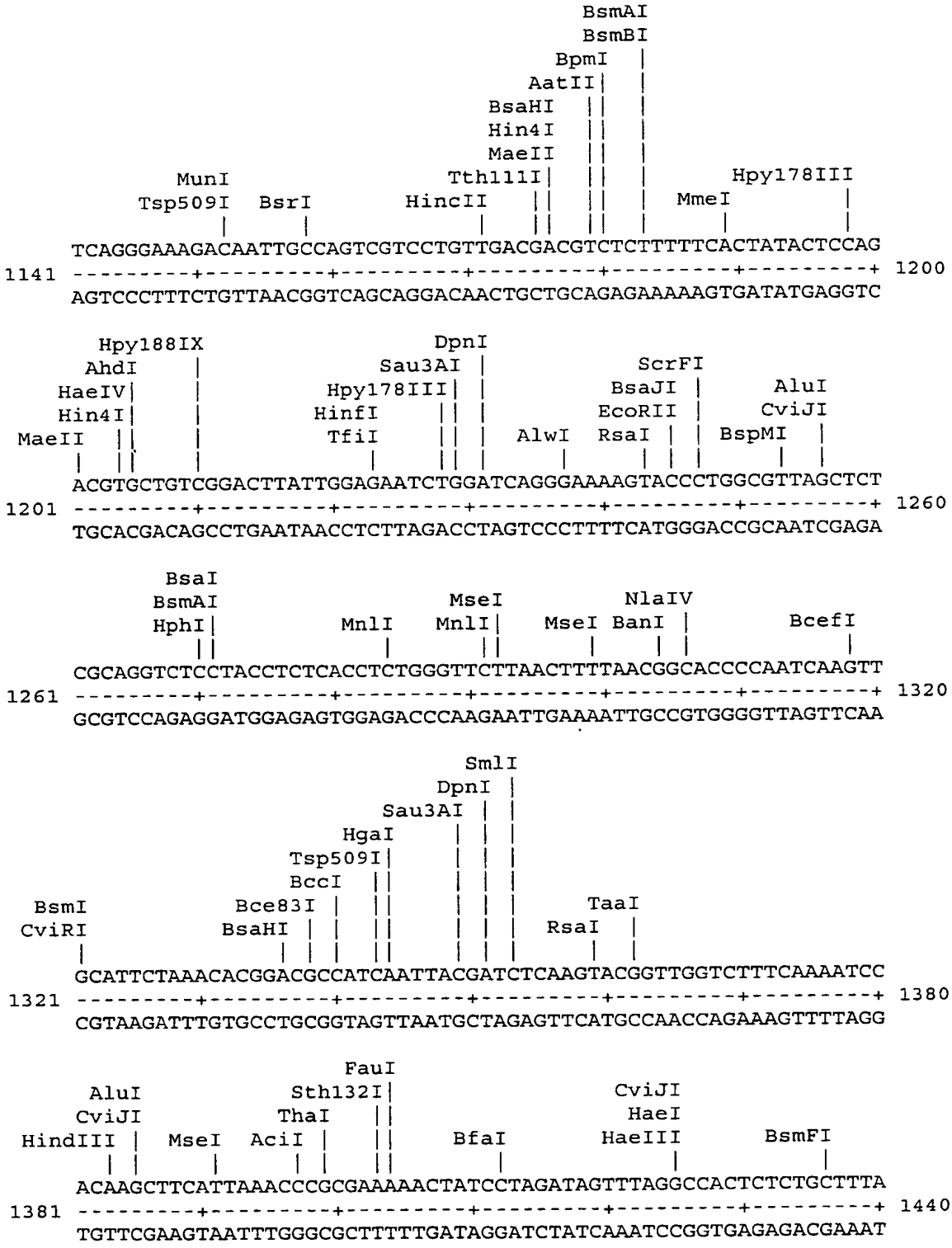
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Fig. 14 (con't)

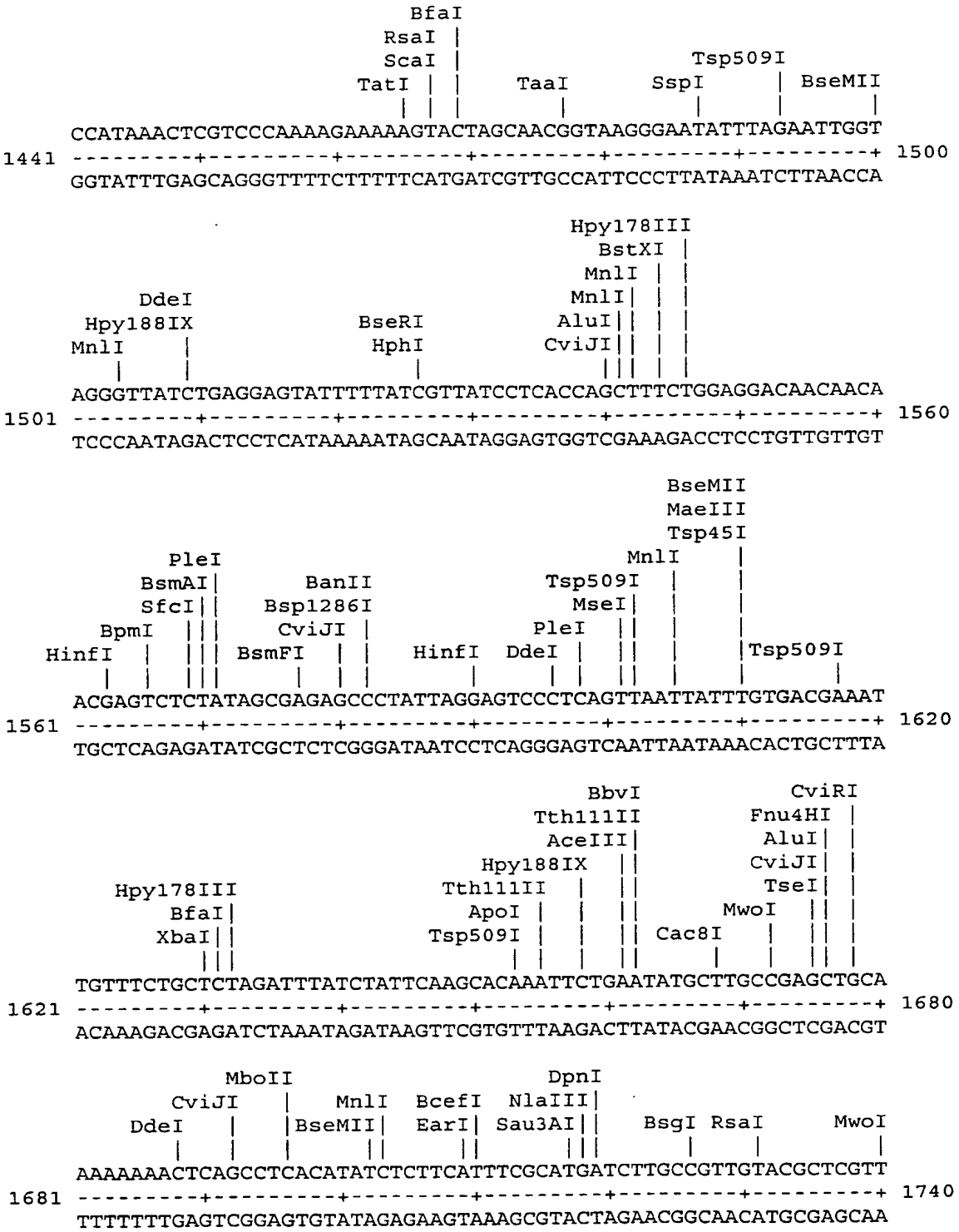
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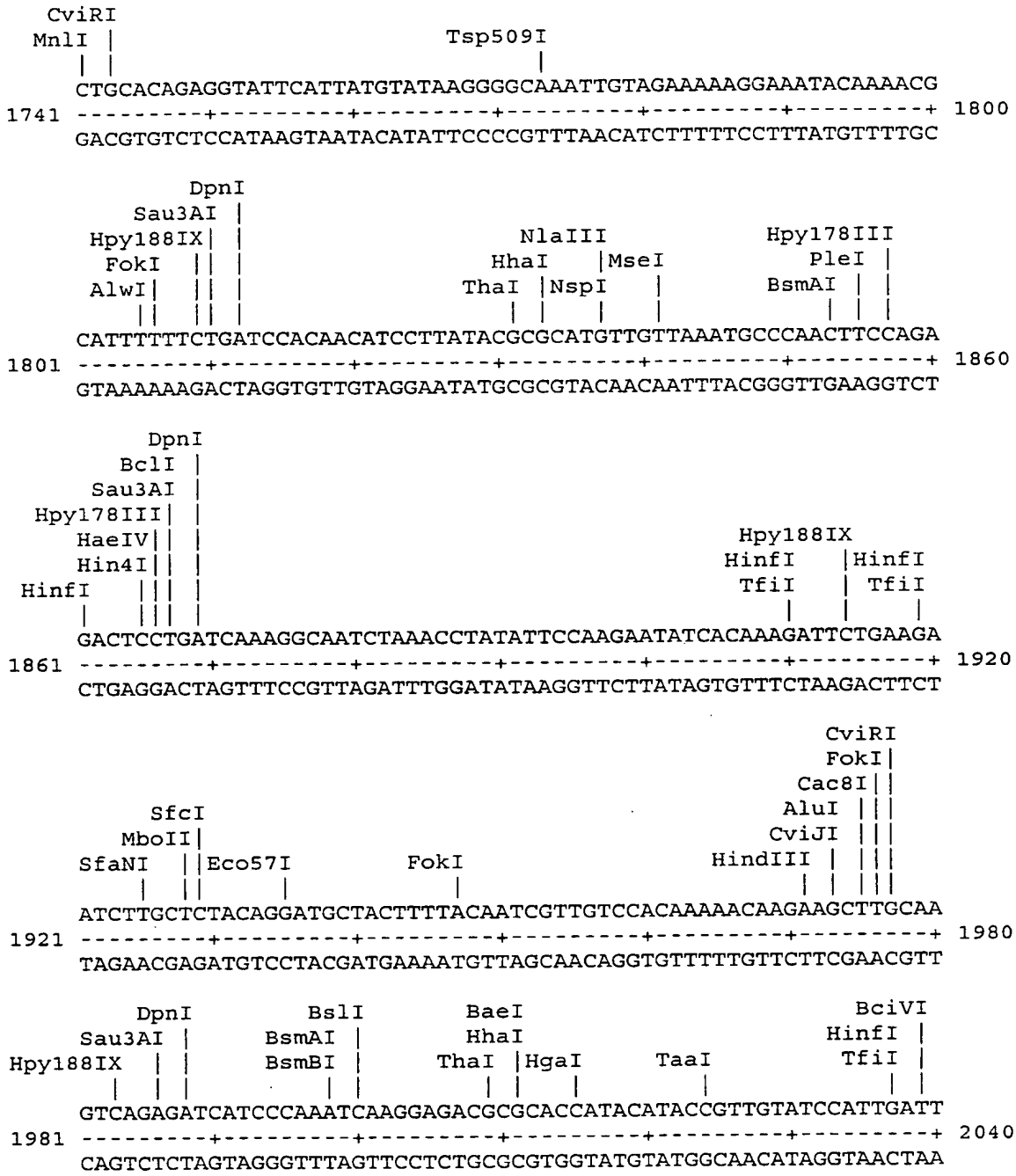
Fig. 14 (con't)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1981
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Fig. 14 (con't)


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AflII
BsaJI
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Figure 15:

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                                            Met Pro Gly Ile Glu
                                              1               5

aaa gca gca aca aca gtg gct gta cct caa gac aaa tct gaa gaa gaa   163
Lys Ala Ala Thr Thr Val Ala Val Pro Gln Asp Lys Ser Glu Glu Glu
                  10                  15                  20

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Lys Val Lys Glu Arg Leu Thr Lys Arg Glu Leu Thr Cys Glu Asp Leu
              25                  30                  35

aaa gat aac ggc tat act gtc aat ttt gaa gac att tct att tta gag   259
Lys Asp Asn Gly Tyr Thr Val Asn Phe Glu Asp Ile Ser Ile Leu Glu
          40                  45                  50

ttg ttg cag ttc gta agt aaa att tct gga acg aac ttt gtc ttt gat   307
Leu Leu Gln Phe Val Ser Lys Ile Ser Gly Thr Asn Phe Val Phe Asp
      55                  60                  65

agc aac gat ttg caa ttc aat gtc acg atc gtt tcc cac gat cct act   355
Ser Asn Asp Leu Gln Phe Asn Val Thr Ile Val Ser His Asp Pro Thr
  70                  75                  80                  85

tct gta gat gat tta tct aca atc tta cta caa gtc tta aaa atg cat   403
Ser Val Asp Asp Leu Ser Thr Ile Leu Leu Gln Val Leu Lys Met His
                  90                  95                 100

gac ttg aag gtt gtt gaa caa ggc aat aac gtc ctt atc tat cgt aat   451
Asp Leu Lys Val Val Glu Gln Gly Asn Asn Val Leu Ile Tyr Arg Asn
              105                 110                 115

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Pro His Leu Ser Lys Leu Ser Thr Val Val Thr Asp Ser Ser Leu Lys
          120                 125                 130

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Glu Thr Cys Glu Ala Val Val Val Thr Arg Val Phe Arg Leu Tyr Arg
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Asp Ala Ile Val Ser Ala Ser Glu Ala Thr Arg His Val Ile Ile Ser
                  170                 175                 180

gat att gct ggt aat gtc gat aaa gtc agt gat ttg cta gca gct cta   691
Asp Ile Ala Gly Asn Val Asp Lys Val Ser Asp Leu Leu Ala Ala Leu
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```

Fig. 15 con't)

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        200                 205                 210

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Ala Asn Pro Ala Ala Leu Val Ser Tyr Cys Gln Asp Val Leu Gly Thr
    215                 220                 225

ctg gcc gaa gat gat gct ttc caa atg ttc atc caa cct gga acg aac   835
Leu Ala Glu Asp Asp Ala Phe Gln Met Phe Ile Gln Pro Gly Thr Asn
230                 235                 240                 245

aaa att ttc gtc gtc tct tca cca cgt ctt gca aat aag gca gag cag   883
Lys Ile Phe Val Val Ser Ser Pro Arg Leu Ala Asn Lys Ala Glu Gln
                250                 255                 260

ctc ctg aag tcc tta gat gtc cca gaa atg gca cat acc cta gat gat   931
Leu Leu Lys Ser Leu Asp Val Pro Glu Met Ala His Thr Leu Asp Asp
            265                 270                 275

cct gca agt act gcc ttg gct ttg gga gga aca gga acc acg agc cct   979
Pro Ala Ser Thr Ala Leu Ala Leu Gly Gly Thr Gly Thr Thr Ser Pro
        280                 285                 290

aag agt ttg cgg ttc ttt atg tac aag ctg aag tat caa aat gga gaa   1027
Lys Ser Leu Arg Phe Phe Met Tyr Lys Leu Lys Tyr Gln Asn Gly Glu
    295                 300                 305

gtg att gct aat gcc ctc caa gat atc ggt tac aat cta tat gta acc   1075
Val Ile Ala Asn Ala Leu Gln Asp Ile Gly Tyr Asn Leu Tyr Val Thr
310                 315                 320                 325

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Thr Ala Met Asp Glu Asp Phe Ile Asn Thr Leu Asn Ser Ile Gln Trp
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Leu Glu Val Asn Asn Ser Ile Val Ile Ile Gly Asn Gln Gly Asn Val
            345                 350                 355

gac aga gtt att ggc ctc tta aac ggt tta gat tta cct cct aaa cag   1219
Asp Arg Val Ile Gly Leu Leu Asn Gly Leu Asp Leu Pro Pro Lys Gln
        360                 365                 370

gtt tac atc gaa gtt tta att cta gat acc agc tta gag aaa tcc tgg   1267
Val Tyr Ile Glu Val Leu Ile Leu Asp Thr Ser Leu Glu Lys Ser Trp
    375                 380                 385

gac ttt gga gtg caa tgg gta gcc cta ggt gat gaa caa agt aaa gta   1315
Asp Phe Gly Val Gln Trp Val Ala Leu Gly Asp Glu Gln Ser Lys Val
390                 395                 400                 405
```

Fig. 15 con't)

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gct tat gct tct gga cta ttg aat aat act ggc ata gcc aca cct aca   1363
Ala Tyr Ala Ser Gly Leu Leu Asn Asn Thr Gly Ile Ala Thr Pro Thr
                410                 415                 420

aaa gca act gtc cct ccc ggc acg cca aat cct ggt tcg atc cct ctt   1411
Lys Ala Thr Val Pro Pro Gly Thr Pro Asn Pro Gly Ser Ile Pro Leu
            425                 430                 435

cct acg cca gga caa ttg aca ggg ttc tca gat atg ctg aac tct tcg   1459
Pro Thr Pro Gly Gln Leu Thr Gly Phe Ser Asp Met Leu Asn Ser Ser
        440                 445                 450

tca gca ttc ggt cta gga atc atc gga aat gtc cta agt cat aaa ggg   1507
Ser Ala Phe Gly Leu Gly Ile Ile Gly Asn Val Leu Ser His Lys Gly
    455                 460                 465

aag tct ttc ctt act ttg gga ggc tta tta agt gcc tta gat caa gat   1555
Lys Ser Phe Leu Thr Leu Gly Gly Leu Leu Ser Ala Leu Asp Gln Asp
470                 475                 480                 485

gga gat act gtc att gtc ttg aat cct aga atc atg gct cag gat acg   1603
Gly Asp Thr Val Ile Val Leu Asn Pro Arg Ile Met Ala Gln Asp Thr
                490                 495                 500

caa caa gct tcg ttt ttt gta ggg caa acg gtc cct tac caa act atc   1651
Gln Gln Ala Ser Phe Phe Val Gly Gln Thr Val Pro Tyr Gln Thr Ile
            505                 510                 515

aaa tac tat atc caa gaa aca gga act gta acg caa aat atc gat tat   1699
Lys Tyr Tyr Ile Gln Glu Thr Gly Thr Val Thr Gln Asn Ile Asp Tyr
        520                 525                 530

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Glu Asp Ile Gly Val Asn Leu Val Val Thr Ser Thr Val Ala Pro Asn
    535                 540                 545

aat gta gtt aca cta caa atc gaa cag acg atc tca gaa tta cat tcc   1795
Asn Val Val Thr Leu Gln Ile Glu Gln Thr Ile Ser Glu Leu His Ser
550                 555                 560                 565

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Arg Asp Lys Thr Thr Lys Val Val Ser Gly Val Pro Leu Leu Asn Ser
        600                 605                 610
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Fig. 15 con't)

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Lys Arg Asn Ile Met Met Phe Ile Lys Pro Lys Val Ile Ser Ser Phe
630                 635                 640                 645

gaa gaa ggc act cgt gtt acc aat aag gaa gga tac aga tac aat tgg   2083
Glu Glu Gly Thr Arg Val Thr Asn Lys Glu Gly Tyr Arg Tyr Asn Trp
                650                 655                 660

gaa gct gat gaa gga tcc atg caa gtg gcc cct cgc cat gct cct gaa   2131
Glu Ala Asp Glu Gly Ser Met Gln Val Ala Pro Arg His Ala Pro Glu
            665                 670                 675

tgc caa gga cct cct tct tta cag gct gaa agt gac ttt aaa ata ata   2179
Cys Gln Gly Pro Pro Ser Leu Gln Ala Glu Ser Asp Phe Lys Ile Ile
        680                 685                 690

gaa ata gaa gct cag tagtggtata taaaagagga agatgatatt ctccgccgtg   2234
Glu Ile Glu Ala Gln
    695

gaatagcttc tgactctgtt gcattcaggg ggaaagccaa gaagatgtag agtcggccgt 2294

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Figure 16 (RY-41)

Restriction enzyme analysis of CPN100538

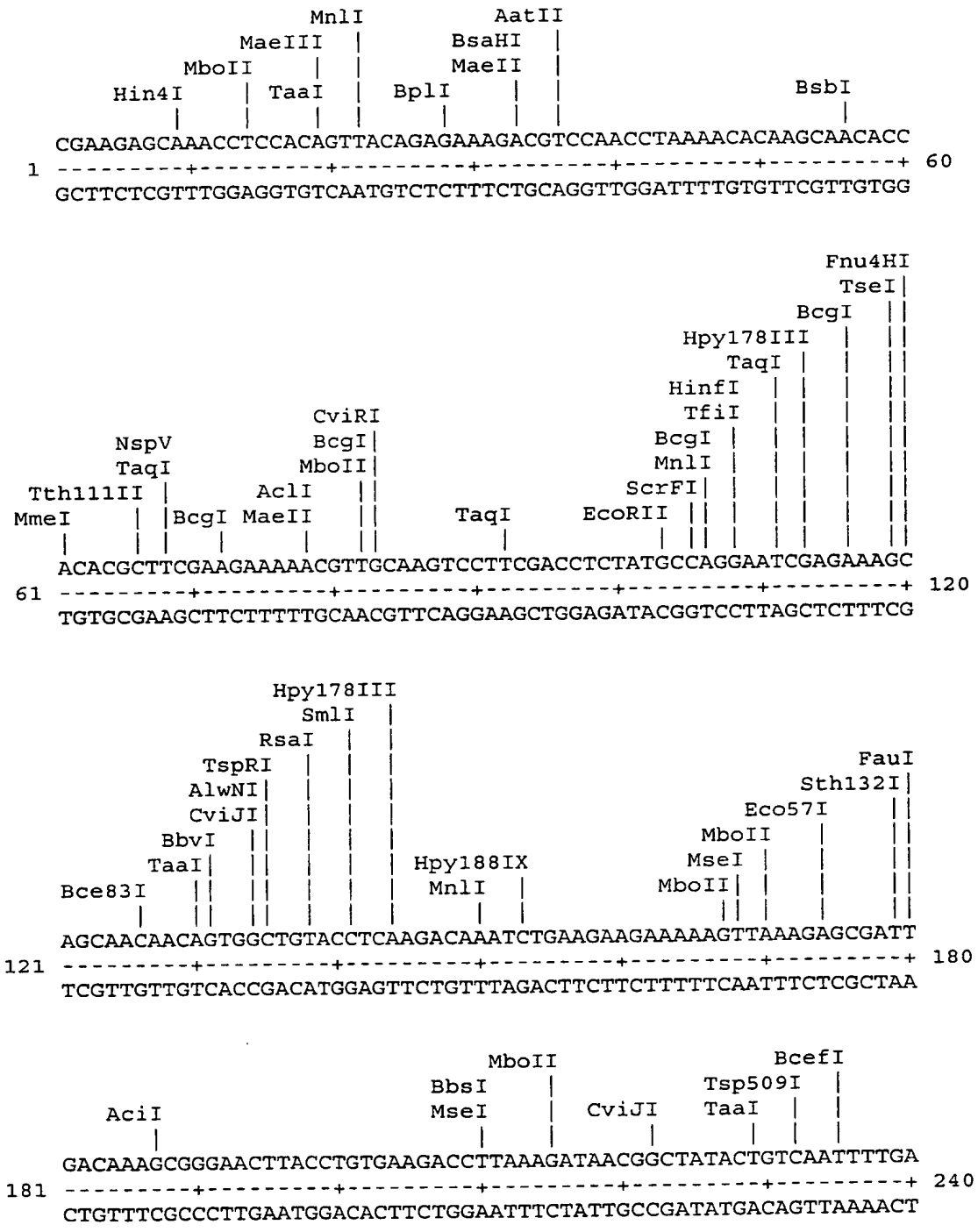
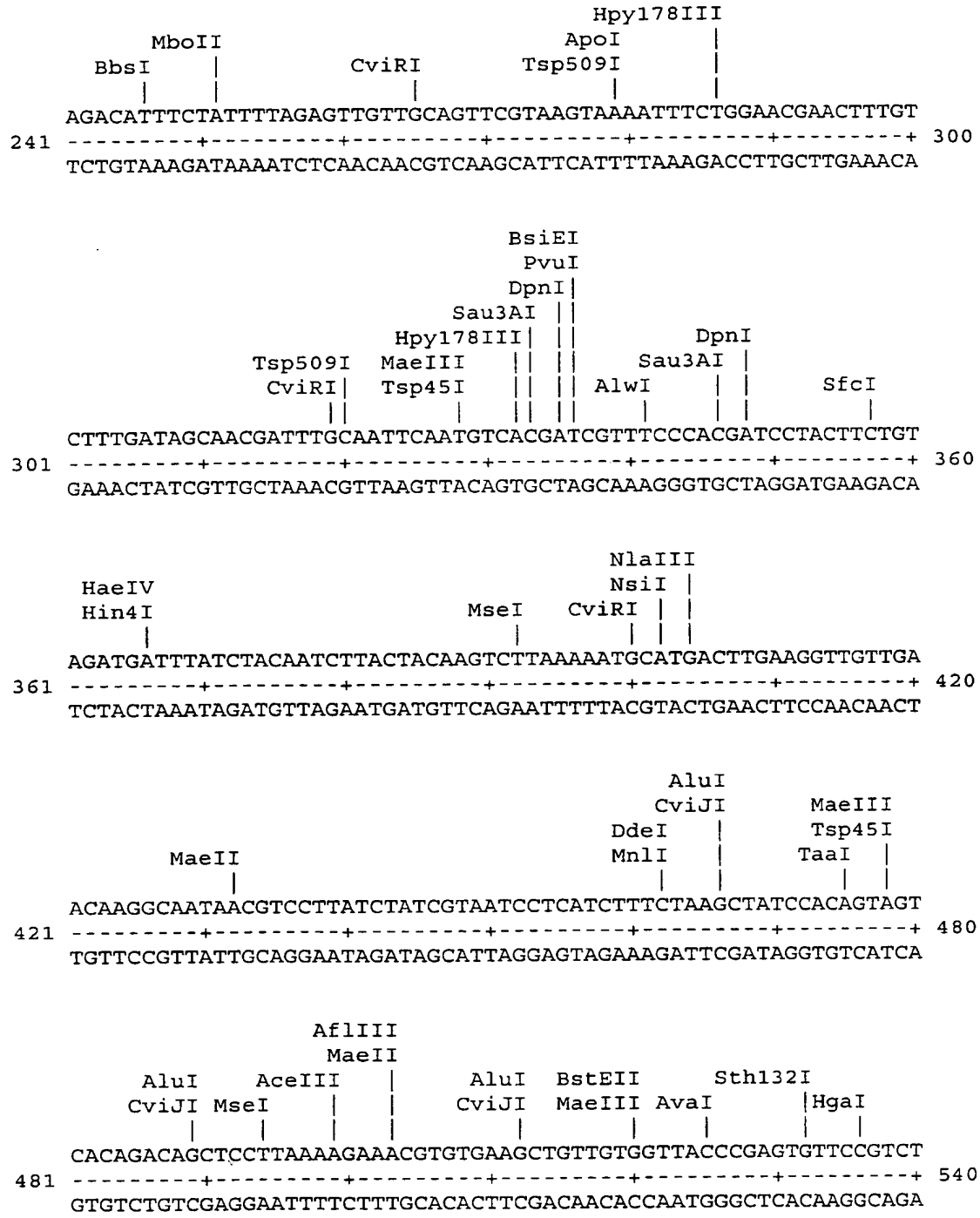


Fig. 16 (con't)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PvuI
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Tsp45I
MaeII
MnlI
TaaI
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421
480
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MaeII
AluI
AceIII
AluI
BstEII
Sth132I
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MseI
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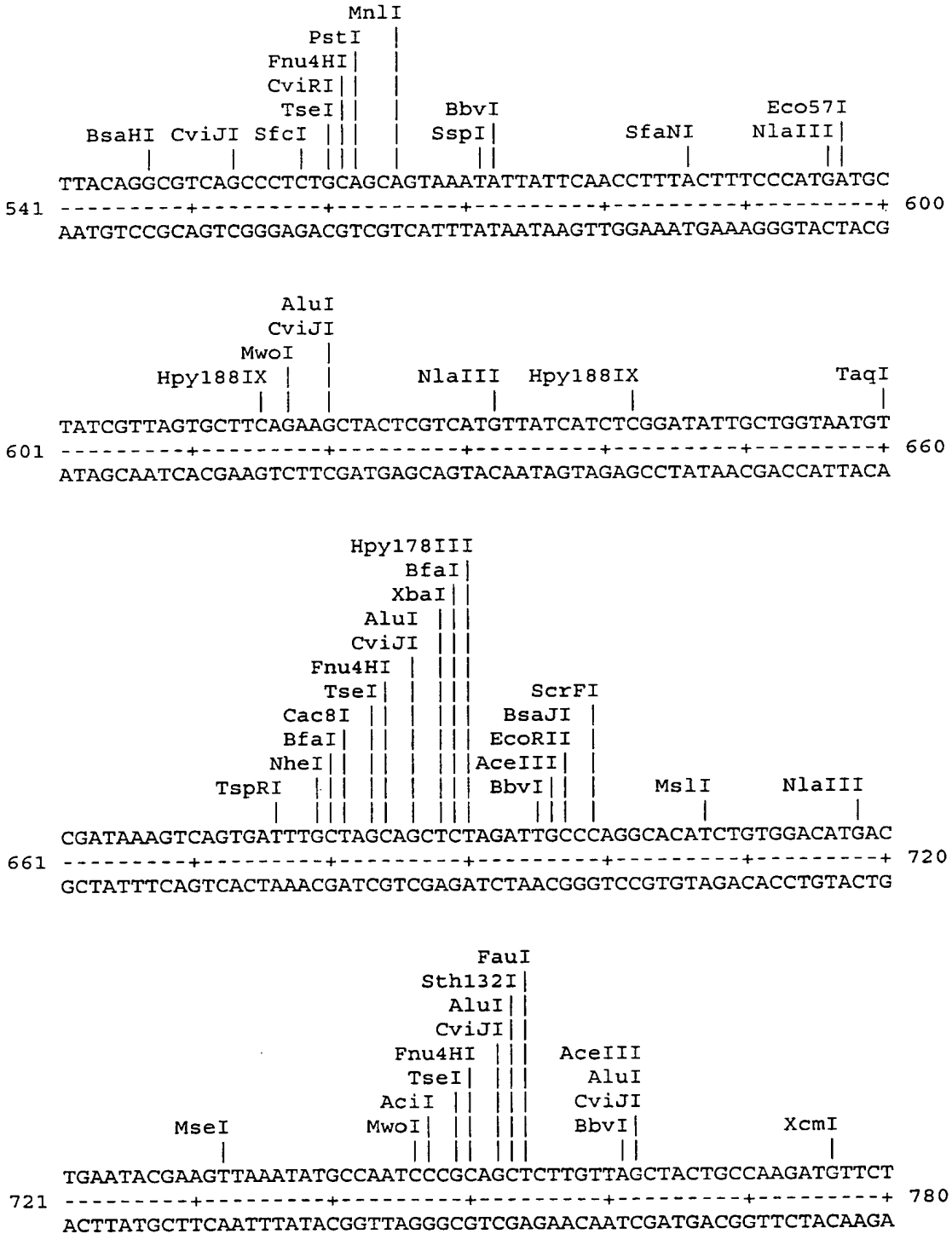
Fig. 16 (con't)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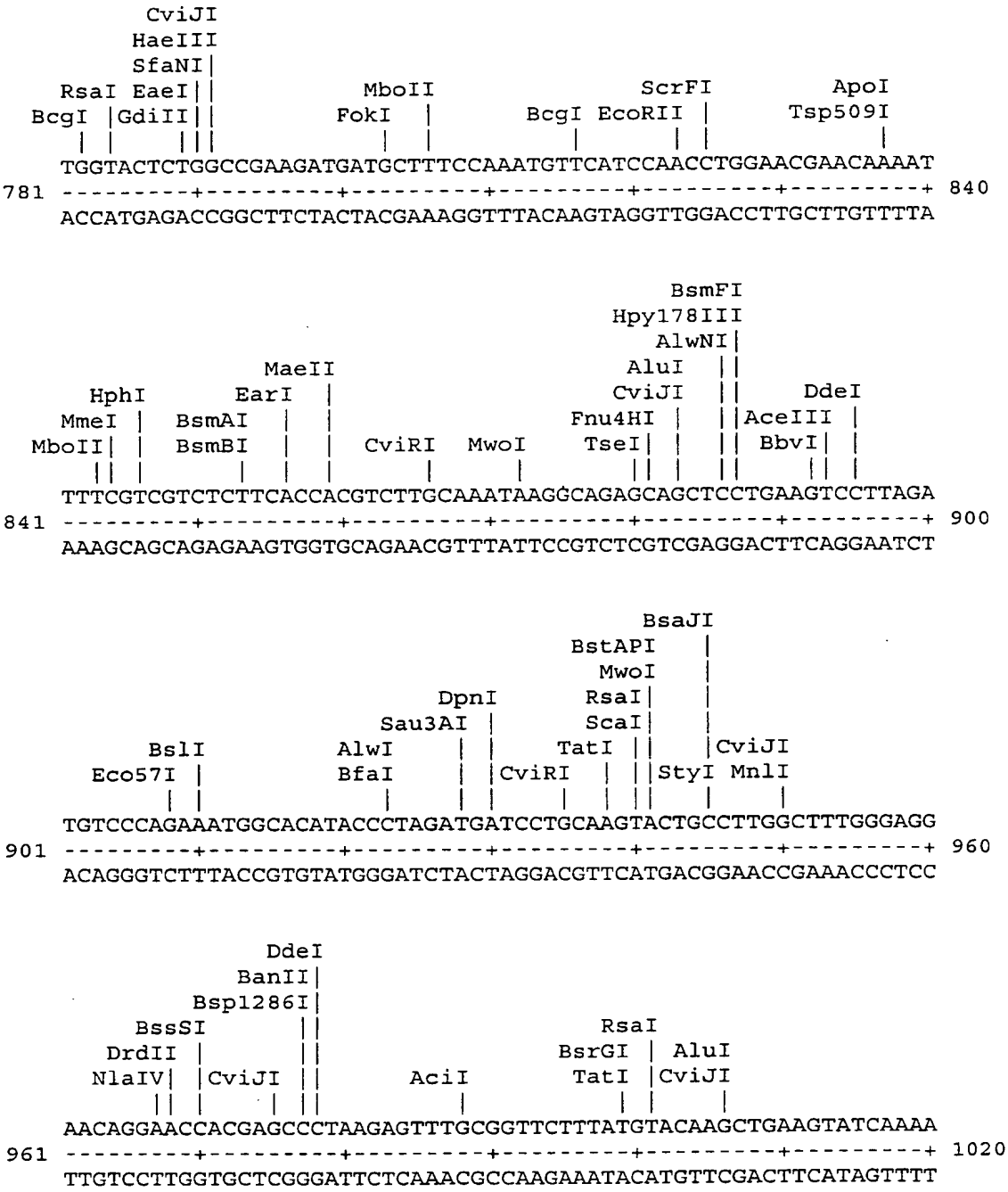
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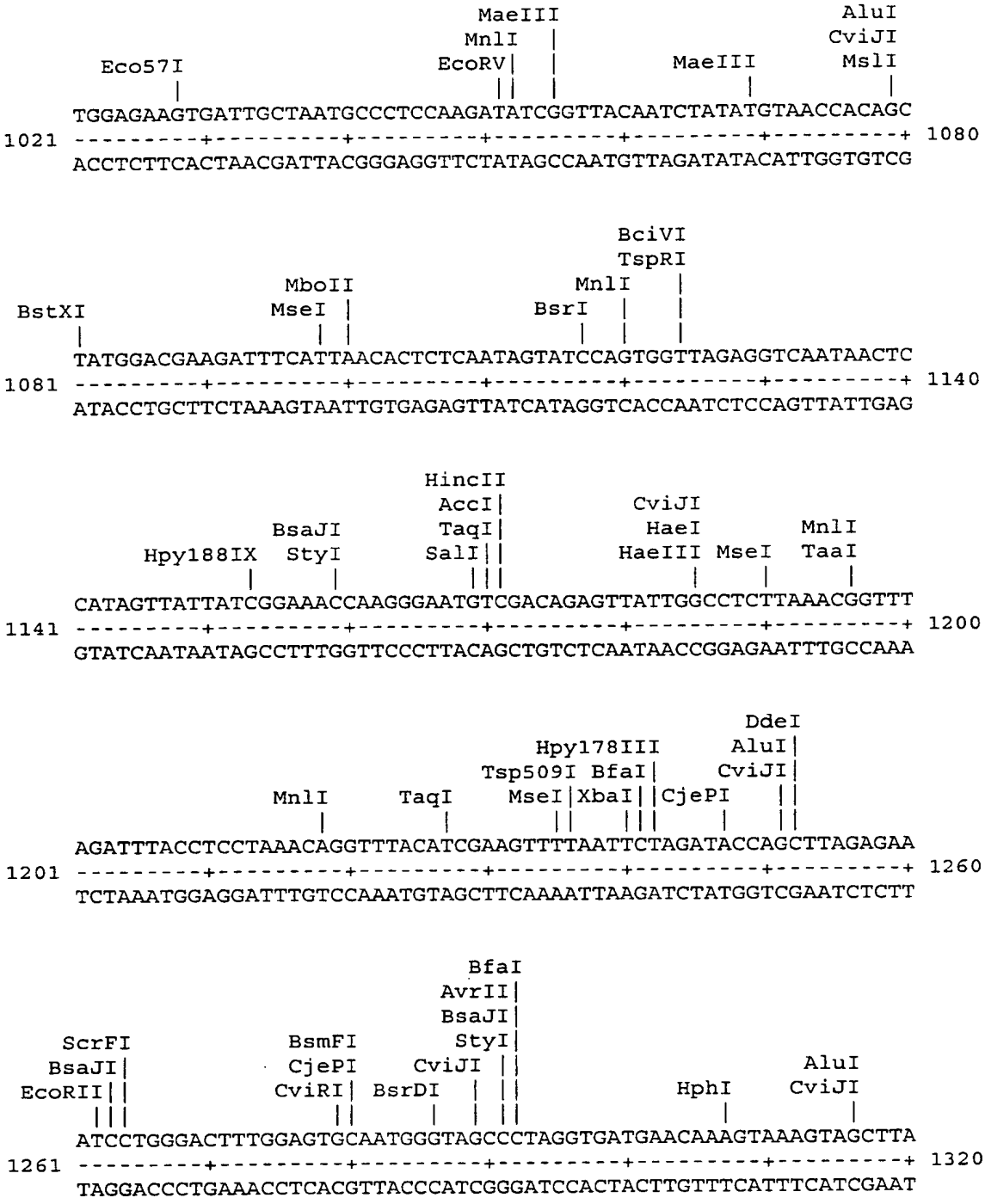
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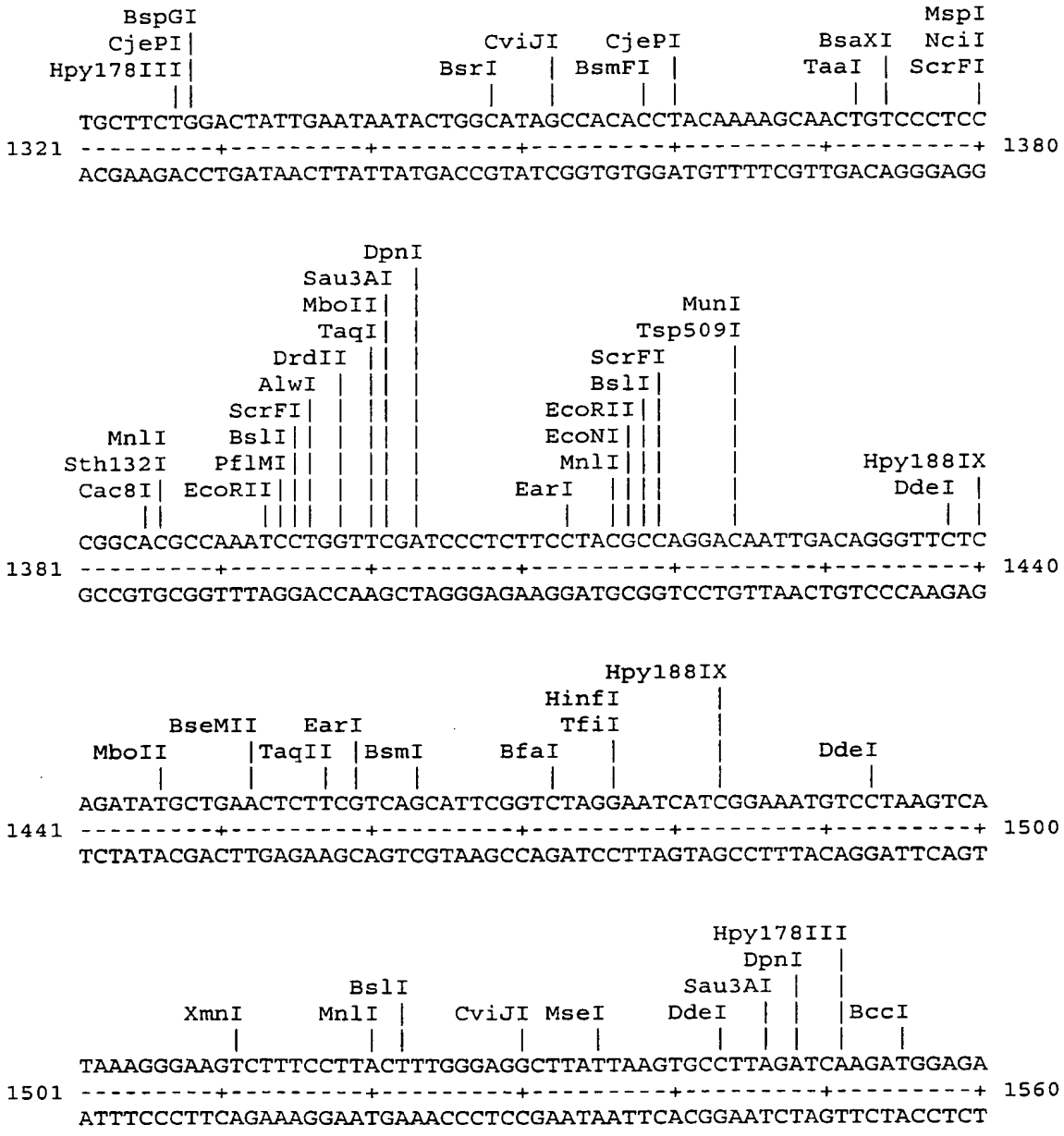
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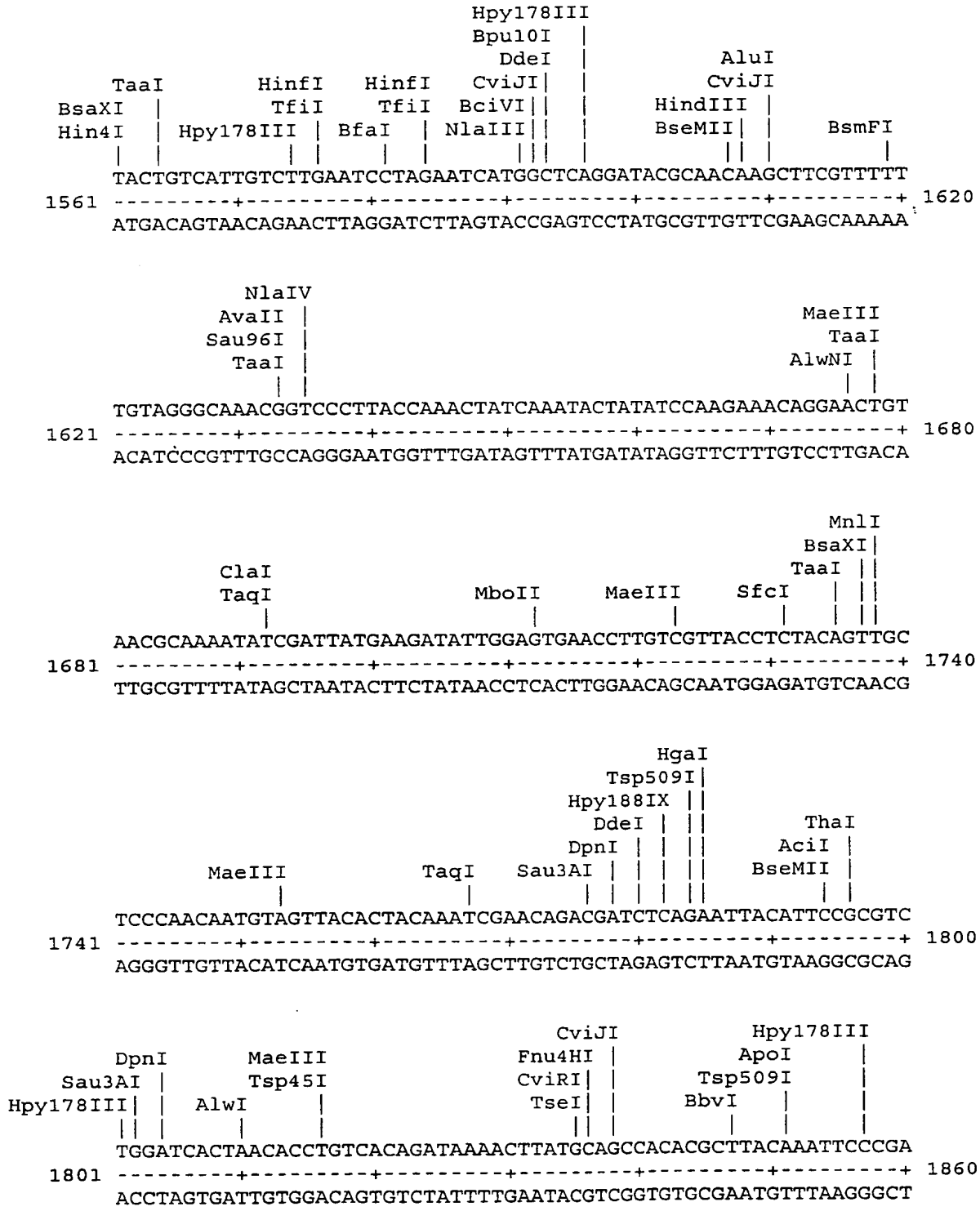
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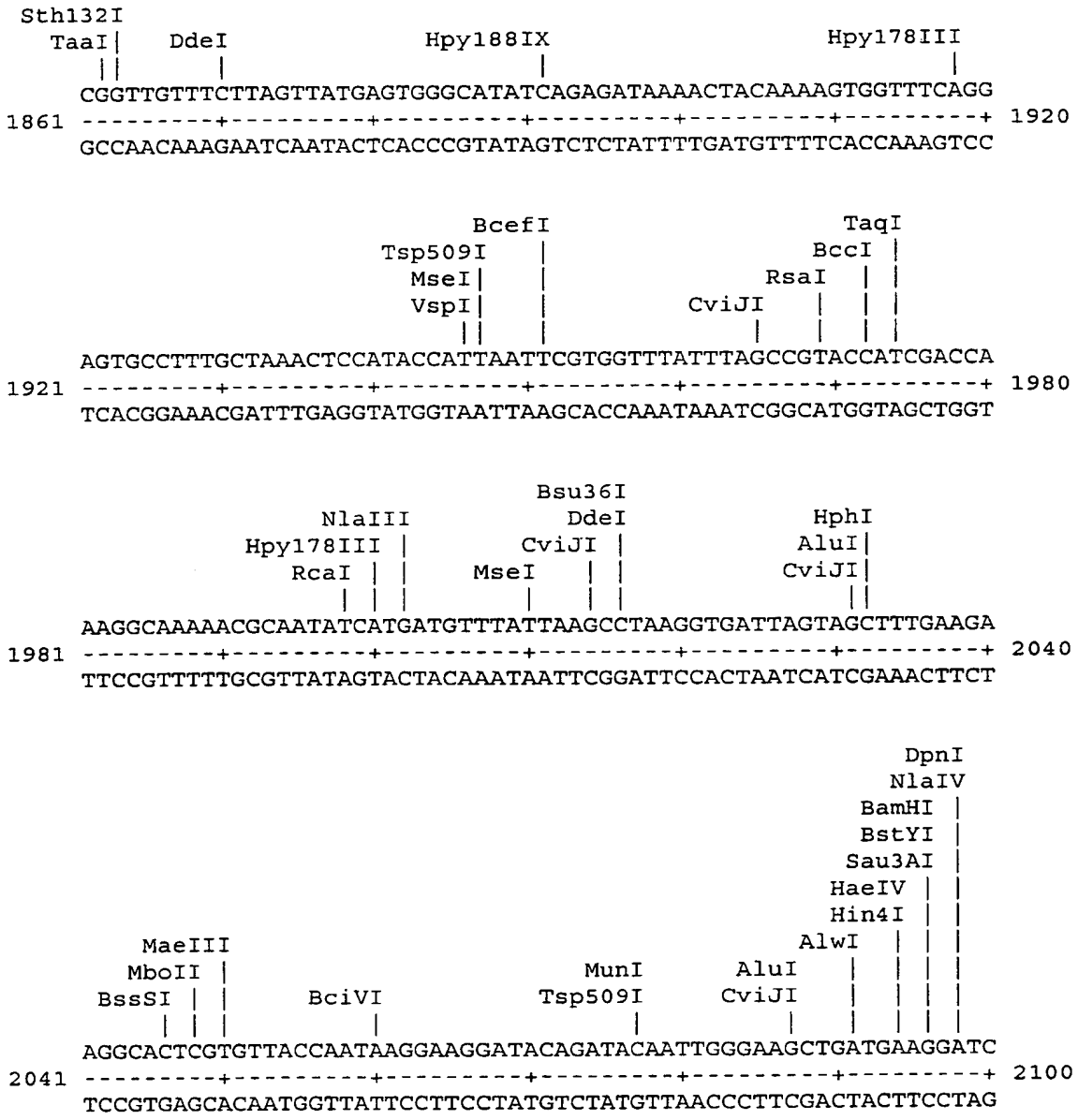
Fig. 16 (con't)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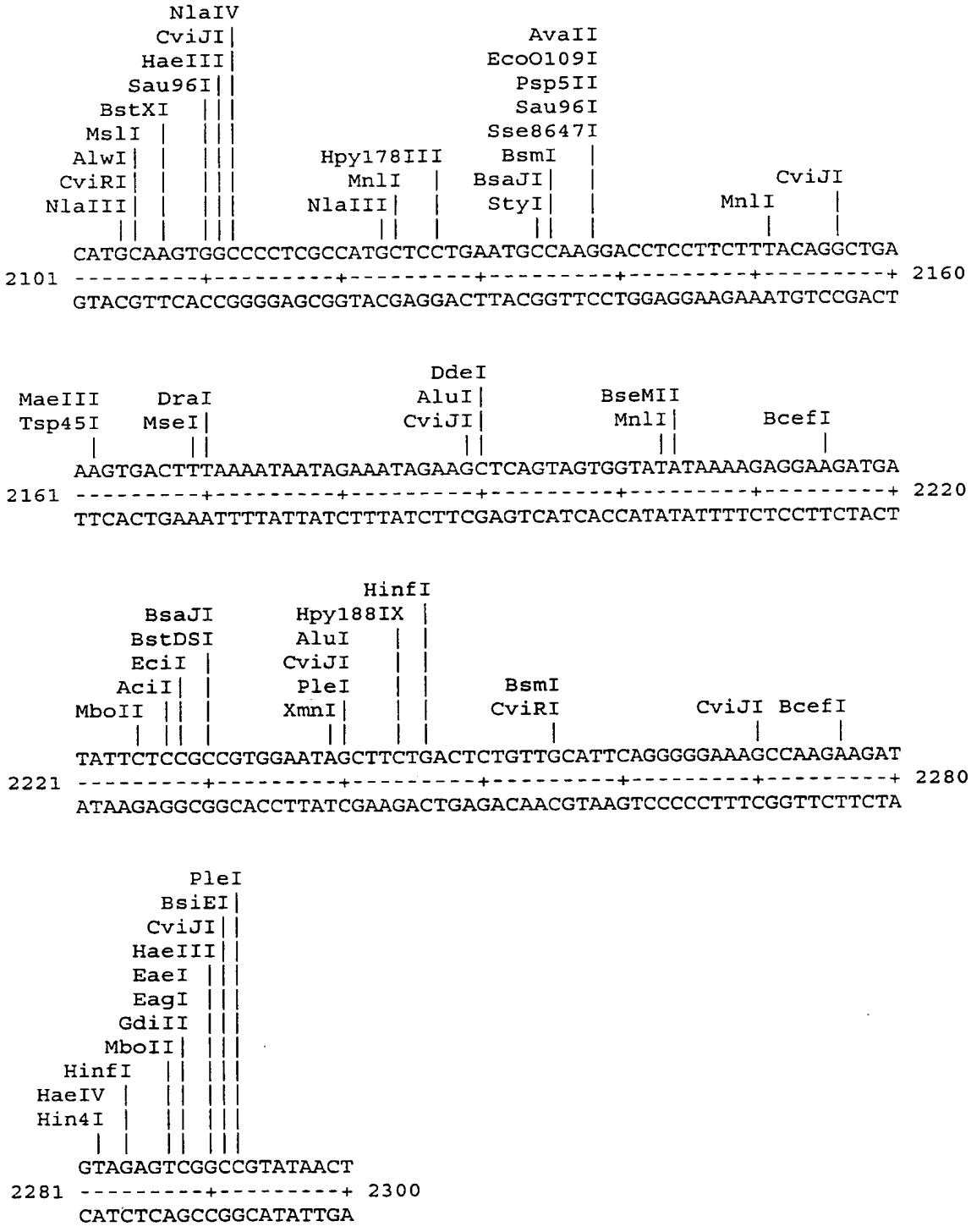
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Figure 17: CPN100557

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aac gtt gaa gag ggg act tac gat atg att ctc ctt act atg ata ctc    499
Asn Val Glu Glu Gly Thr Tyr Asp Met Ile Leu Leu Thr Met Ile Leu
Asn Val Glu Glu Gly Thr Tyr Asp Met Ile Leu Leu Thr Met Ile Leu
         120                 125                 130

ttg ccc tgt ggc att ttc tta atg atg tac aat gta aac ggc gct ttg    547
Leu Pro Cys Gly Ile Phe Leu Met Met Tyr Asn Val Asn Gly Ala Leu
Leu Pro Cys Gly Ile Phe Leu Met Met Tyr Asn Val Asn Gly Ala Leu
     135                 140                 145

ctt cac tgt gga aat aag ttt ttc ggg gtg gga tta gct ccc gta gtt    595
Leu His Cys Gly Asn Lys Phe Phe Gly Val Gly Leu Ala Pro Val Val
Leu His Cys Gly Asn Lys Phe Phe Gly Val Gly Leu Ala Pro Val Val
150                 155                 160                 165

gta aat atc att tgg att ttc ttt gtt ata gcg gct cgt cat tca gat    643
Val Asn Ile Ile Trp Ile Phe Phe Val Ile Ala Ala Arg His Ser Asp
Val Asn Ile Ile Trp Ile Phe Phe Val Ile Ala Ala Arg His Ser Asp
                 170                 175                 180
```

Fig. 17 (con't)

```
cct aga gag cgt att atc ggt tta tcc gtg gct cta gtt atc ggg ttt    691
Pro Arg Glu Arg Ile Ile Gly Leu Ser Val Ala Leu Val Ile Gly Phe
Pro Arg Glu Arg Ile Ile Gly Leu Ser Val Ala Leu Val Ile Gly Phe
            185                 190                 195

ttc ttc gaa tgg tta atc acg gtt cct gga gta tgg aaa ttt cta tta    739
Phe Phe Glu Trp Leu Ile Thr Val Pro Gly Val Trp Lys Phe Leu Leu
Phe Phe Glu Trp Leu Ile Thr Val Pro Gly Val Trp Lys Phe Leu Leu
        200                 205                 210

gaa gcg aag agc cca cct caa gaa cac gat agt gtt cga gct tta tta    787
Glu Ala Lys Ser Pro Pro Gln Glu His Asp Ser Val Arg Ala Leu Leu
Glu Ala Lys Ser Pro Pro Gln Glu His Asp Ser Val Arg Ala Leu Leu
    215                 220                 225

gct ccc tta tct ttg ggt att tta act tca agc atc ttc cag ctg aac    835
Ala Pro Leu Ser Leu Gly Ile Leu Thr Ser Ser Ile Phe Gln Leu Asn
Ala Pro Leu Ser Leu Gly Ile Leu Thr Ser Ser Ile Phe Gln Leu Asn
230                 235                 240                 245

ctt ctt tct gat atc tgc ttg gct cgc tat gta cat gaa ata ggc cct    883
Leu Leu Ser Asp Ile Cys Leu Ala Arg Tyr Val His Glu Ile Gly Pro
Leu Leu Ser Asp Ile Cys Leu Ala Arg Tyr Val His Glu Ile Gly Pro
                250                 255                 260

cta tat ctt atg tac tcc tta aag att tat cag ctc ccc ata cat ctc    931
Leu Tyr Leu Met Tyr Ser Leu Lys Ile Tyr Gln Leu Pro Ile His Leu
Leu Tyr Leu Met Tyr Ser Leu Lys Ile Tyr Gln Leu Pro Ile His Leu
            265                 270                 275

ttt ggc ttt ggt gtg ttt acc gtt ctc ctc cca gca att tct cgt tgt    979
Phe Gly Phe Gly Val Phe Thr Val Leu Leu Pro Ala Ile Ser Arg Cys
Phe Gly Phe Gly Val Phe Thr Val Leu Leu Pro Ala Ile Ser Arg Cys
        280                 285                 290

gta cag cga gaa gat cat gag agg gga ttg aaa ctt atg aag ttc gtt   1027
Val Gln Arg Glu Asp His Glu Arg Gly Leu Lys Leu Met Lys Phe Val
Val Gln Arg Glu Asp His Glu Arg Gly Leu Lys Leu Met Lys Phe Val
    295                 300                 305

ctc acc cta acc atg tcc gta atg atc att atg aca gca ggg cta ttg   1075
Leu Thr Leu Thr Met Ser Val Met Ile Ile Met Thr Ala Gly Leu Leu
Leu Thr Leu Thr Met Ser Val Met Ile Ile Met Thr Ala Gly Leu Leu
310                 315                 320                 325

ctc tta gct tta cct gga gtc cgt gtc ctt tat gaa cac gga ctt ttc   1123
Leu Leu Ala Leu Pro Gly Val Arg Val Leu Tyr Glu His Gly Leu Phe
Leu Leu Ala Leu Pro Gly Val Arg Val Leu Tyr Glu His Gly Leu Phe
                330                 335                 340

cct cag agt gct gtc tac gct att gtt cgt gta ttg cga ggt tat ggt   1171
Pro Gln Ser Ala Val Tyr Ala Ile Val Arg Val Leu Arg Gly Tyr Gly
Pro Gln Ser Ala Val Tyr Ala Ile Val Arg Val Leu Arg Gly Tyr Gly
            345                 350                 355

gcc agt att atc cct atg gcc ttg gct cct tta gtc tct gtt ctt ttt   1219
Ala Ser Ile Ile Pro Met Ala Leu Ala Pro Leu Val Ser Val Leu Phe
Ala Ser Ile Ile Pro Met Ala Leu Ala Pro Leu Val Ser Val Leu Phe
        360                 365                 370
```

Fig. 17 (con't)

```
tat gca cag cgg cag tat gct gtt ccg ctc ttt ata gga atc ggt acg   1267
Tyr Ala Gln Arg Gln Tyr Ala Val Pro Leu Phe Ile Gly Ile Gly Thr
Tyr Ala Gln Arg Gln Tyr Ala Val Pro Leu Phe Ile Gly Ile Gly Thr
    375                 380                 385

gct ttg gcc aat att gtt tta agc ttg gtt cta ggt cgt tgg gtt tta   1315
Ala Leu Ala Asn Ile Val Leu Ser Leu Val Leu Gly Arg Trp Val Leu
Ala Leu Ala Asn Ile Val Leu Ser Leu Val Leu Gly Arg Trp Val Leu
390                 395                 400                 405

aaa gac gtc tcg ggc att tcc tat gct aca tcc ata act gct tgg gtg   1363
Lys Asp Val Ser Gly Ile Ser Tyr Ala Thr Ser Ile Thr Ala Trp Val
Lys Asp Val Ser Gly Ile Ser Tyr Ala Thr Ser Ile Thr Ala Trp Val
                410                 415                 420

cag tta tat ttc ctc tgg tat tat tct tcg aaa aga ctc cct atg tac   1411
Gln Leu Tyr Phe Leu Trp Tyr Tyr Ser Ser Lys Arg Leu Pro Met Tyr
Gln Leu Tyr Phe Leu Trp Tyr Tyr Ser Ser Lys Arg Leu Pro Met Tyr
            425                 430                 435

tct aag tta ctt tgg gag agc atc cgg cgt tcc ata aaa gtt atg gga   1459
Ser Lys Leu Leu Trp Glu Ser Ile Arg Arg Ser Ile Lys Val Met Gly
Ser Lys Leu Leu Trp Glu Ser Ile Arg Arg Ser Ile Lys Val Met Gly
        440                 445                 450

acc act atg ctt gct tgt atg att act cta ggc tta aat atc ctt acg   1507
Thr Thr Met Leu Ala Cys Met Ile Thr Leu Gly Leu Asn Ile Leu Thr
Thr Thr Met Leu Ala Cys Met Ile Thr Leu Gly Leu Asn Ile Leu Thr
    455                 460                 465

caa act aca tat gta att ttc tta aac ccc ctc aca cca ctt gct tgg   1555
Gln Thr Thr Tyr Val Ile Phe Leu Asn Pro Leu Thr Pro Leu Ala Trp
Gln Thr Thr Tyr Val Ile Phe Leu Asn Pro Leu Thr Pro Leu Ala Trp
470                 475                 480                 485

ccc tta tcc tcc ata acg gct caa gca att gct ttt tta tct gag agc   1603
Pro Leu Ser Ser Ile Thr Ala Gln Ala Ile Ala Phe Leu Ser Glu Ser
Pro Leu Ser Ser Ile Thr Ala Gln Ala Ile Ala Phe Leu Ser Glu Ser
                490                 495                 500

tgc att ttc ttg gct ttt ttg ttt ggt ttt gca aaa ctg ctt cga gta   1651
Cys Ile Phe Leu Ala Phe Leu Phe Gly Phe Ala Lys Leu Leu Arg Val
Cys Ile Phe Leu Ala Phe Leu Phe Gly Phe Ala Lys Leu Leu Arg Val
            505                 510                 515

gaa gat ctt att aat ttg gct tct ttt gaa tac tgg cgt ggg caa cgg   1699
Glu Asp Leu Ile Asn Leu Ala Ser Phe Glu Tyr Trp Arg Gly Gln Arg
Glu Asp Leu Ile Asn Leu Ala Ser Phe Glu Tyr Trp Arg Gly Gln Arg
        520                 525                 530

ggt ctt ttg caa aga caa cac gtg atg caa gac act caa aat           1741
Gly Leu Leu Gln Arg Gln His Val Met Gln Asp Thr Gln Asn
Gly Leu Leu Gln
    535                 540                 545

taatcatgtt tgtttcttgt agctcagtcg ctttctttta gctttaagtt ttgatagcct 1801

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tatcaatggt tagcgagtgt ggttctttta gcgctgaca                        1900
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Figure 18 (RY-43)

Restriction enzyme analysis of CPN100557

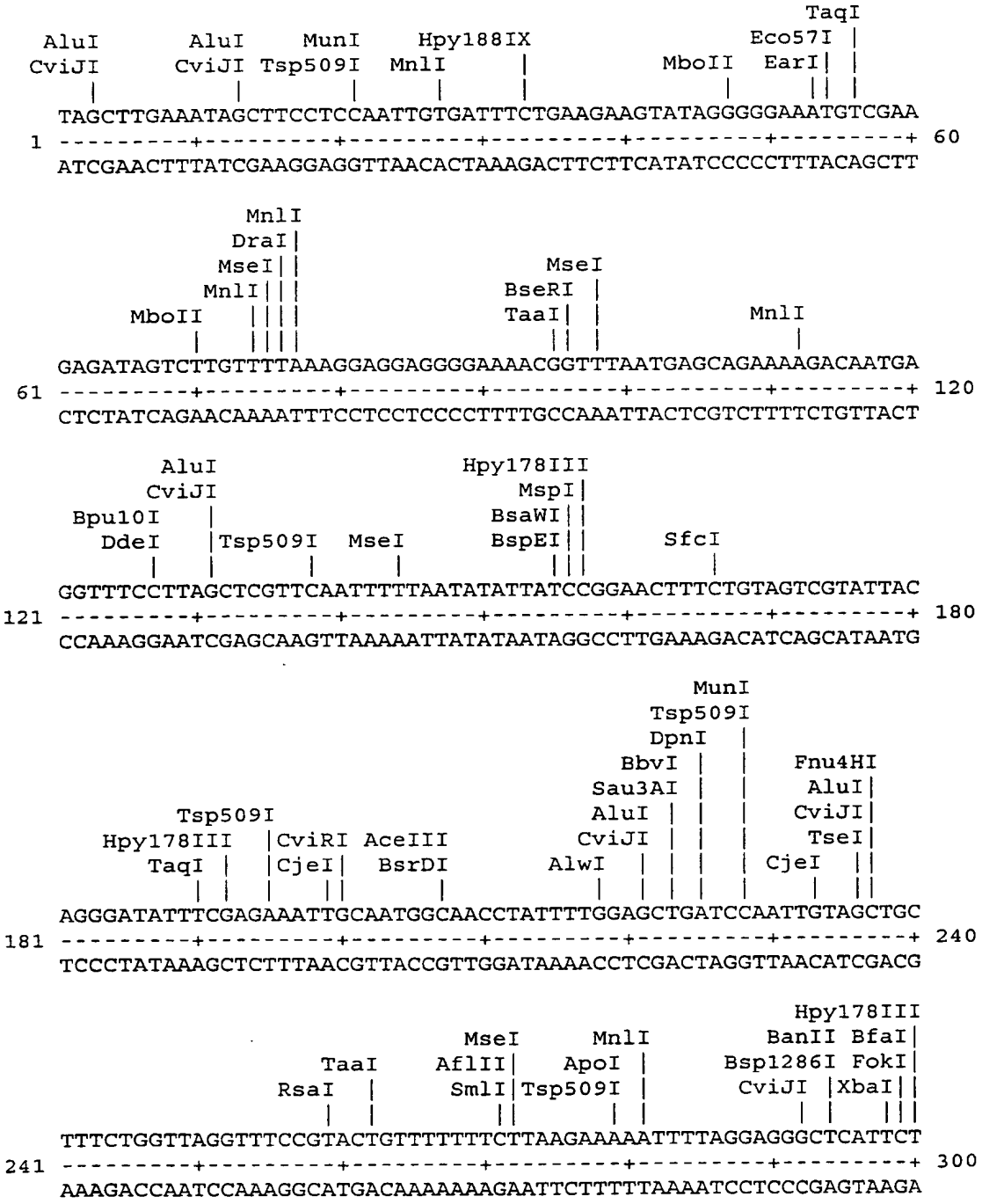

Fig. 18 (con't)

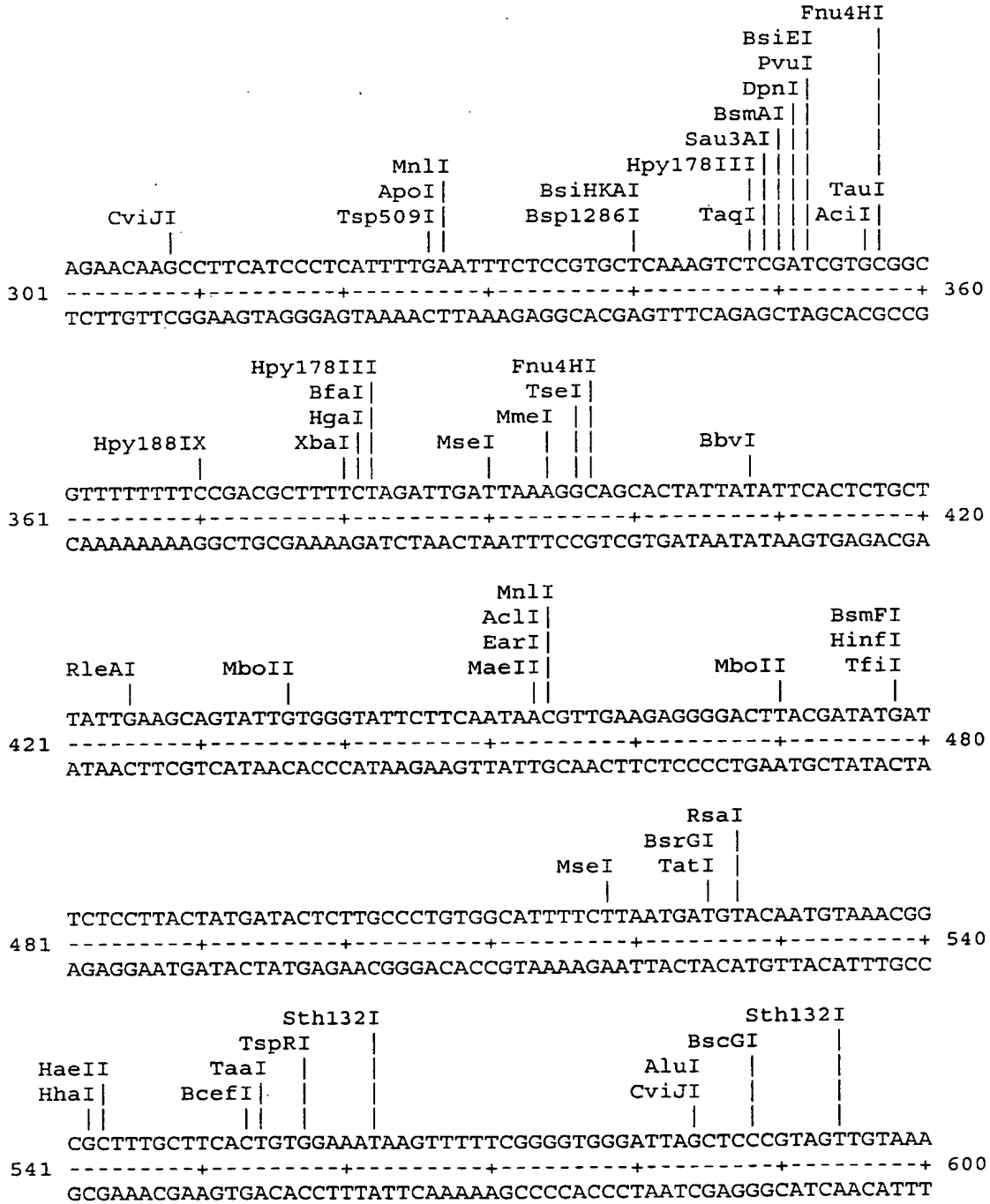
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Fig. 18 (con't)

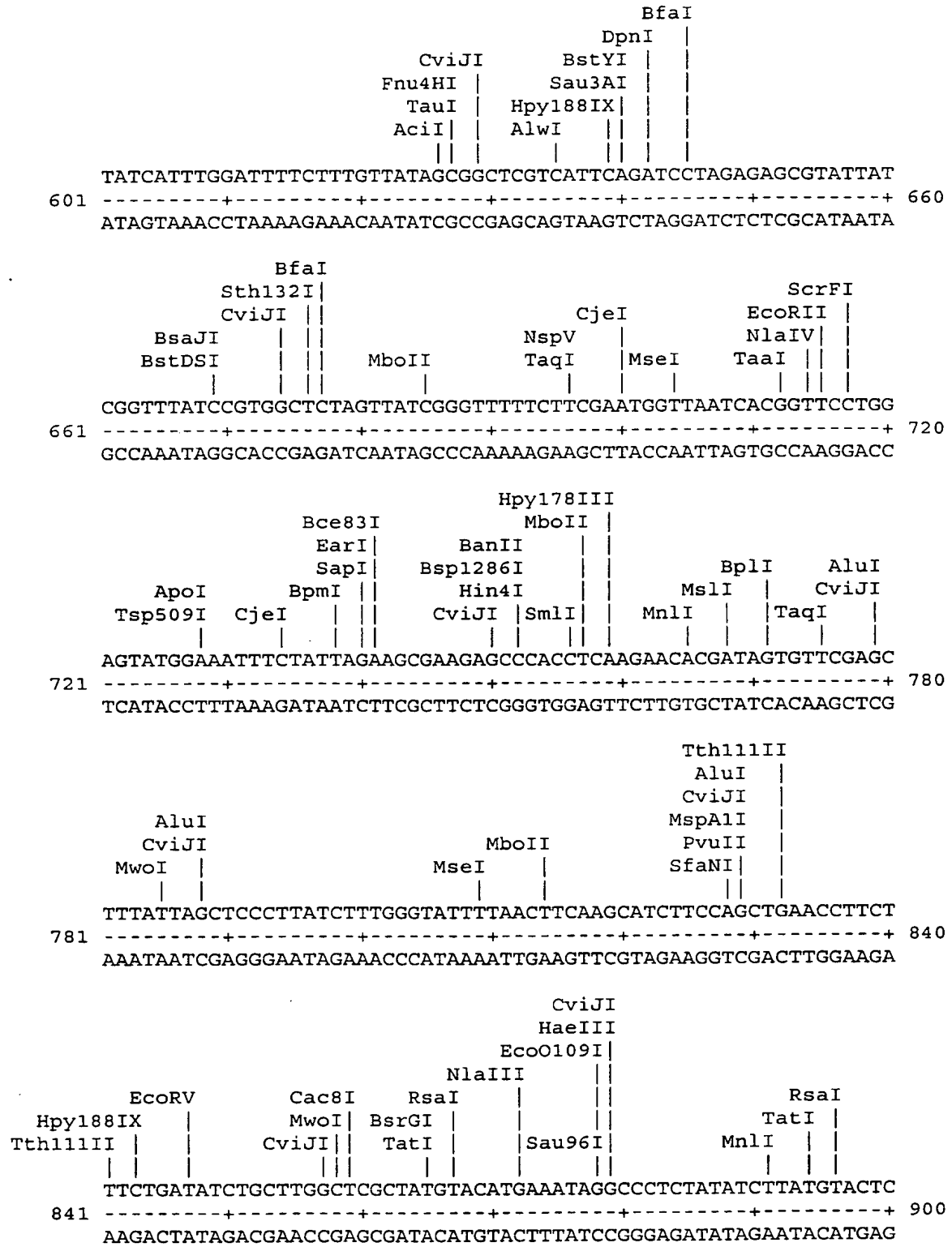
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Fig. 18 (con't)

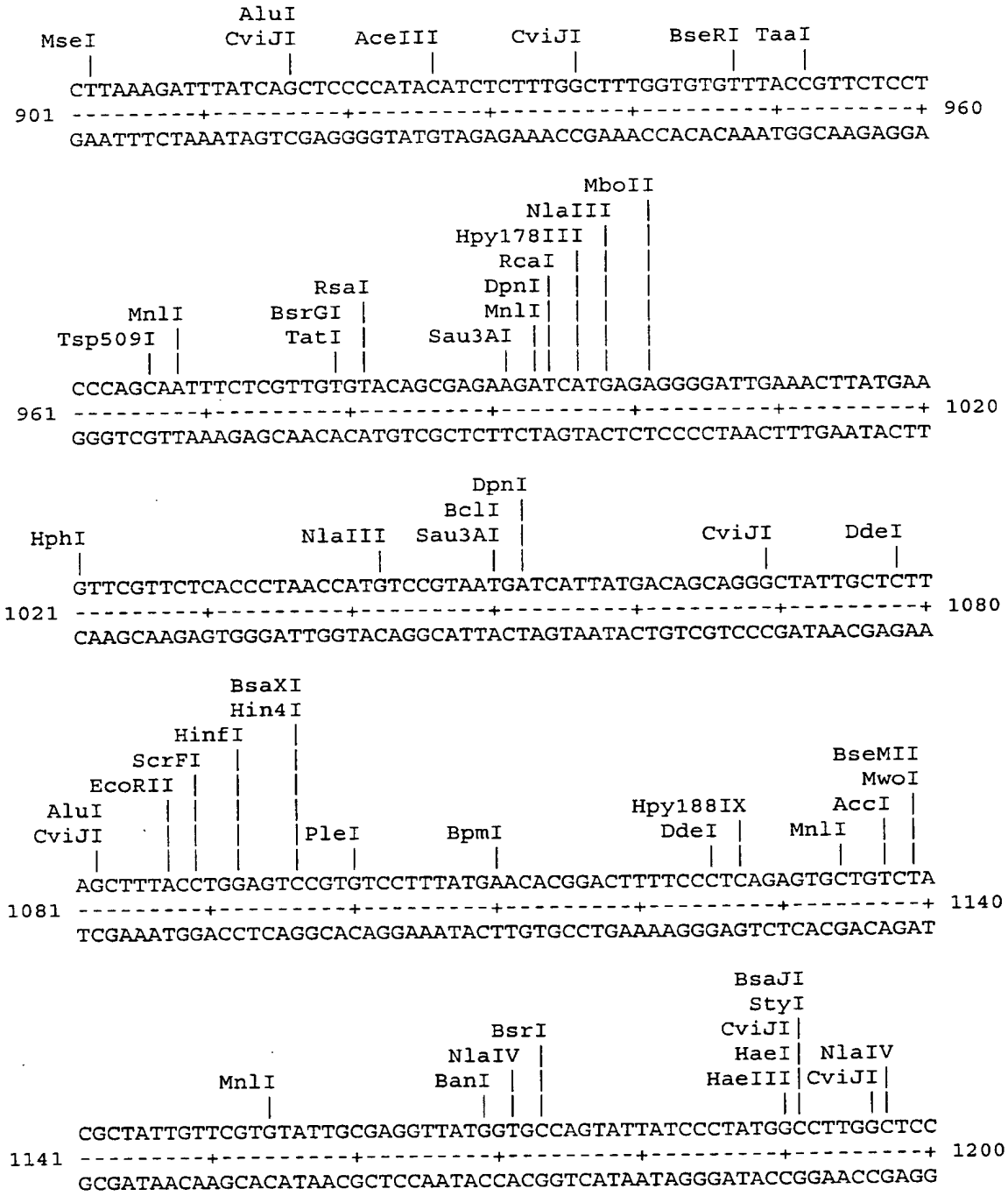
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Fig. 18 (con't)

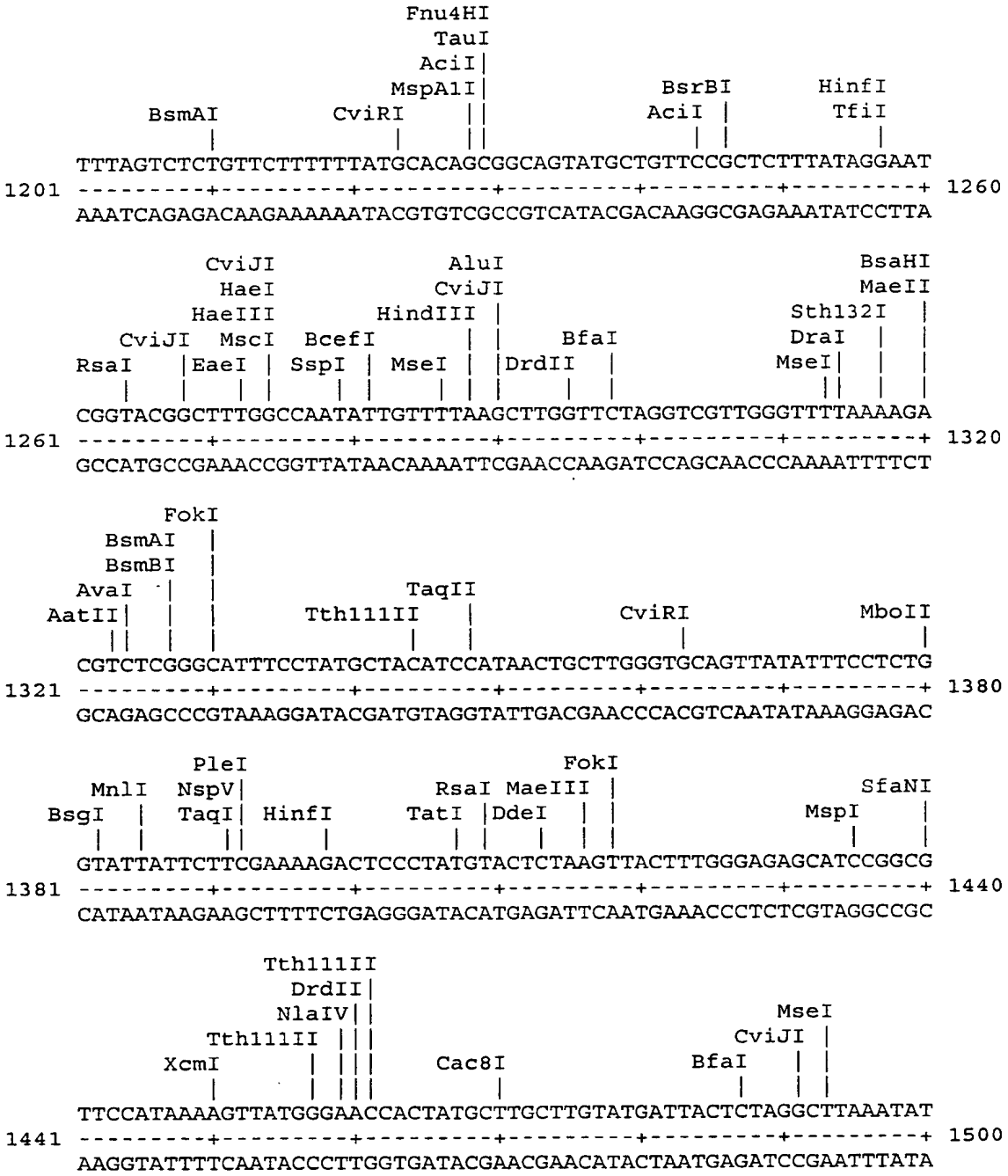
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Fig. 18 (con't)

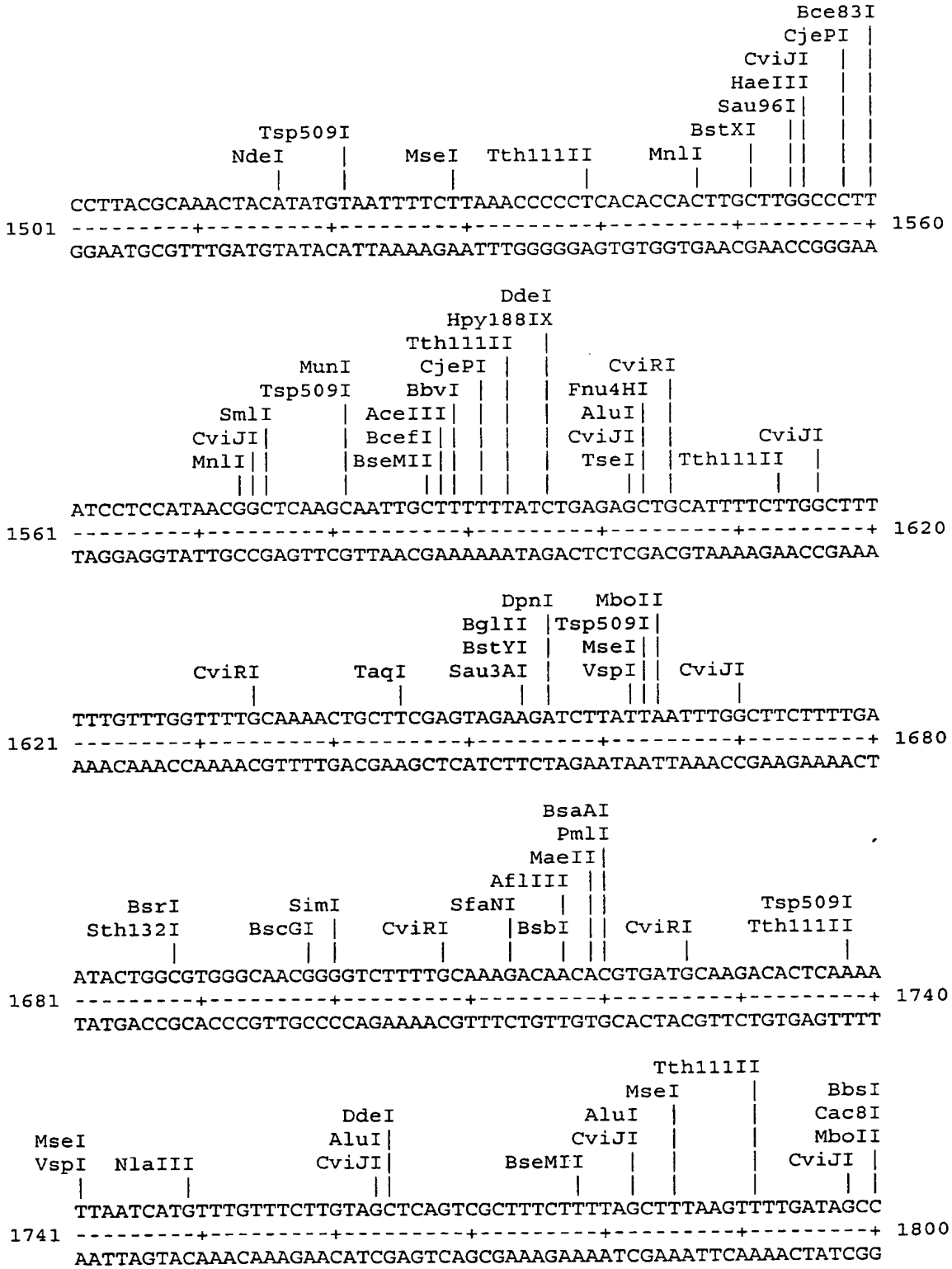
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Fig. 18 (con't)

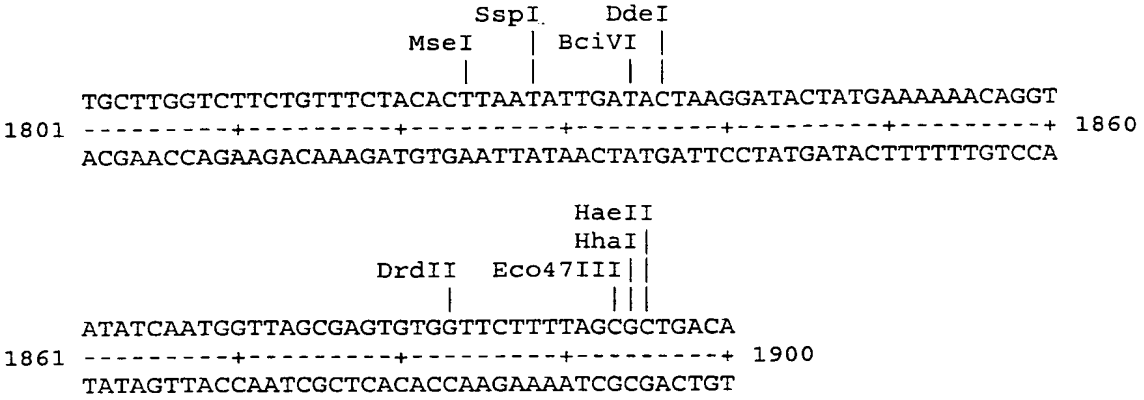
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Figure 19: CPN100622

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                                            Met Lys Thr Ser Arg
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Asn Lys Gln Cys Lys Ile Thr Asp Pro Leu Ser Lys Ser Ser Phe Phe
                 10                  15                  20

gtt gga gcc tta att tta ggt aaa act aca ata ctc ctt aat gcg act   211
Val Gly Ala Leu Ile Leu Gly Lys Thr Thr Ile Leu Leu Asn Ala Thr
             25                  30                  35

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Pro Leu Ser Asp Tyr Phe Asp Asn Gln Ala Asn Gln Leu Thr Thr Leu
         40                  45                  50

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Phe Pro Leu Ile Asp Thr Leu Thr Asn Met Thr Pro Tyr Ser His Arg
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gca aca ctt ttt gga gtt agg gat gac act aac caa gac att gtc ctc   355
Ala Thr Leu Phe Gly Val Arg Asp Asp Thr Asn Gln Asp Ile Val Leu
 70                  75                  80                  85

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Asp His Gln Asn Ser Ile Glu Ser Trp Phe Glu Asn Phe Ser Gln Asp
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         120                 125                 130

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     135                 140                 145

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150                 155                 160                 165

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    Thr Gly Gly Ala Val Leu Cys Ser Lys Asn Val Thr Ile Ser Lys
                170                 175                 180

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Asn Gln Gly Thr Ala Tyr Phe Ile Asn Asn Lys Ala Lys Ser Ser Gly
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```

Fig. 19 (con't)

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Gly Ala Ile Gln Ala Ala Ile Ile Asn Ile Lys Asp Asn Thr Gly Pro
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Cys Leu Phe Phe Asn Asn Ala Ala Gly Gly Thr Ala Gly Gly Ala Leu
    215                 220                 225

ttc gct aat gct tgt aga att gag aat aat tct cag cct atc tat ttt   835
Phe Ala Asn Ala Cys Arg Ile Glu Asn Asn Ser Gln Pro Ile Tyr Phe
Phe Ala Asn Ala Cys Arg Ile Glu Asn Asn Ser Gln Pro Ile Tyr Phe
230                 235                 240                 245

ttg aat aac caa tca ggt ctg ggt ggt gca ata aga gta cat caa gag   883
Leu Asn Asn Gln Ser Gly Leu Gly Gly Ala Ile Arg Val His Gln Glu
Leu Asn Asn Gln Ser Gly Leu Gly Gly Ala Ile Arg Val His Gln Glu
                250                 255                 260

tgc att ctt aca aag aat acc ggt tct gtg atc ttc aac aat aat ttt   931
Cys Ile Leu Thr Lys Asn Thr Gly Ser Val Ile Phe Asn Asn Asn Phe
Cys Ile Leu Thr Lys Asn Thr Gly Ser Val Ile Phe Asn Asn Asn Phe
            265                 270                 275

gcc atg gaa gcg gac atc tct gct aac cat tcc tct gga ggg gct atc   979
Ala Met Glu Ala Asp Ile Ser Ala Asn His Ser Ser Gly Gly Ala Ile
Ala Met Glu Ala Asp Ile Ser Ala Asn His Ser Ser Gly Gly Ala Ile
        280                 285                 290

tat tgc att agt tgt tct ata aaa gac aac cca gga att gca gcc ttc   1027
Tyr Cys Ile Ser Cys Ser Ile Lys Asp Asn Pro Gly Ile Ala Ala Phe
Tyr Cys Ile Ser Cys Ser Ile Lys Asp Asn Pro Gly Ile Ala Ala Phe
    295                 300                 305

gat aat aat act gca gca cga gat gga ggt gct atc tgt aca caa tct   1075
Asp Asn Asn Thr Ala Ala Arg Asp Gly Gly Ala Ile Cys Thr Gln Ser
Asp Asn Asn Thr Ala Ala Arg Asp Gly Gly Ala Ile Cys Thr Gln Ser
310                 315                 320                 325

cta act ata caa gac agt ggt ccc gtc tat ttc aca aac aat cag gga   1123
Leu Thr Ile Gln Asp Ser Gly Pro Val Tyr Phe Thr Asn Asn Gln Gly
Leu Thr Ile Gln Asp Ser Gly Pro Val Tyr Phe Thr Asn Asn Gln Gly
                330                 335                 340

act tgg ggc ggc gct atc atg ctc cgt caa gat ggt gca tgc act tta   1171
Thr Trp Gly Gly Ala Ile Met Leu Arg Gln Asp Gly Ala Cys Thr Leu
Thr Trp Gly Gly Ala Ile Met Leu Arg Gln Asp Gly Ala Cys Thr Leu
            345                 350                 355

ttt gct gat cag gga gat att att ttt tat aat aat aga cac ttc aaa   1219
Phe Ala Asp Gln Gly Asp Ile Ile Phe Tyr Asn Asn Arg His Phe Lys
Phe Ala Asp Gln Gly Asp Ile Ile Phe Tyr Asn Asn Arg His Phe Lys
        360                 365                 370

gat act ttc agc aat cat gtt tct gta aac tgc acg cgt aat gtc tca   1267
Asp Thr Phe Ser Asn His Val Ser Val Asn Cys Thr Arg Asn Val Ser
Asp Thr Phe Ser Asn His Val Ser Val Asn Cys Thr Arg Asn Val Ser
    375                 380                 385
```

Fig. 19 (con't)

```
tta aca gtt gga gca agt caa ggt cat tct gct acc ttc tat gat ccc   1315
Leu Thr Val Gly Ala Ser Gln Gly His Ser Ala Thr Phe Tyr Asp Pro
Leu Thr Val Gly Ala Ser Gln Gly His Ser Ala Thr Phe Tyr Asp Pro
390                 395                 400                 405

ata cta caa aga tat act ata caa aac tct atc caa aaa ttt aat cct   1363
Ile Leu Gln Arg Tyr Thr Ile Gln Asn Ser Ile Gln Lys Phe Asn Pro
Ile Leu Gln Arg Tyr Thr Ile Gln Asn Ser Ile Gln Lys Phe Asn Pro
                410                 415                 420

aat cca gaa cac ctc gga act atc ttg ttc tcc tca aca tat att ccg   1411
Asn Pro Glu His Leu Gly Thr Ile Leu Phe Ser Ser Thr Tyr Ile Pro
Asn Pro Glu His Leu Gly Thr Ile Leu Phe Ser Ser Thr Tyr Ile Pro
            425                 430                 435

gat aca tcg act tct cgt gat gac ttc att tca cat ttc aga aac cac   1459
Asp Thr Ser Thr Ser Arg Asp Asp Phe Ile Ser His Phe Arg Asn His
Asp Thr Ser Thr Ser Arg Asp Asp Phe Ile Ser His Phe Arg Asn His
        440                 445                 450

att gga ctg tac aac ggc aca ctc gct ctt gaa gat cga gca gag tgg   1507
Ile Gly Leu Tyr Asn Gly Thr Leu Ala Leu Glu Asp Arg Ala Glu Trp
Ile Gly Leu Tyr Asn Gly Thr Leu Ala Leu Glu Asp Arg Ala Glu Trp
    455                 460                 465

aaa gtc tat aaa ttt gat caa ttt ggt ggg act cta cgg tta ggc agt   1555
Lys Val Tyr Lys Phe Asp Gln Phe Gly Gly Thr Leu Arg Leu Gly Ser
Lys Val Tyr Lys Phe Asp Gln Phe Gly Gly Thr Leu Arg Leu Gly Ser
470                 475                 480                 485

aga gct gtg ttt tct aca aca gac gaa gaa caa agt agc agt agt gtg   1603
Arg Ala Val Phe Ser Thr Thr Asp Glu Glu Gln Ser Ser Ser Ser Val
Arg Ala Val Phe Ser Thr Thr Asp Glu Glu Gln Ser Ser Ser Ser Val
                490                 495                 500

ggt tct gta att aac atc aat aat ctt gca att aac ctt ccc tct atc   1651
Gly Ser Val Ile Asn Ile Asn Asn Leu Ala Ile Asn Leu Pro Ser Ile
Gly Ser Val Ile Asn Ile Asn Asn Leu Ala Ile Asn Leu Pro Ser Ile
            505                 510                 515

tta ggc aac aga gtt gct ccc aag cta tgg att cgc ccc aca ggt tca   1699
Leu Gly Asn Arg Val Ala Pro Lys Leu Trp Ile Arg Pro Thr Gly Ser
Leu Gly Asn Arg Val Ala Pro Lys Leu Trp Ile Arg Pro Thr Gly Ser
        520                 525                 530

tca gca ccc tat agc gaa gat aat aac cct ata atc aat ctc tca gga   1747
Ser Ala Pro Tyr Ser Glu Asp Asn Asn Pro Ile Ile Asn Leu Ser Gly
Ser Ala Pro Tyr Ser Glu Asp Asn Asn Pro Ile Ile Asn Leu Ser Gly
    535                 540                 545

cct ttg agc cta ctg gat gac gag aac cta gat ccc tat gat act gca   1795
Pro Leu Ser Leu Leu Asp Asp Glu Asn Leu Asp Pro Tyr Asp Thr Ala
Pro Leu Ser Leu Leu Asp Asp Glu Asn Leu Asp Pro Tyr Asp Thr Ala
550                 555                 560                 565

gac ctt gcc caa cct atc gca gaa gtt cct ctt ctg tat ctc tta gac   1843
Asp Leu Ala Gln Pro Ile Ala Glu Val Pro Leu Leu Tyr Leu Leu Asp
Asp Leu Ala Gln Pro Ile Ala Glu Val Pro Leu Leu Tyr Leu Leu Asp
                570                 575                 580
```

Fig. 19 (con't)

```
tac agc aac cac cat atc aaa gca tct gga tat tct gga aaa ata caa   2467
Tyr Ser Asn His His Ile Lys Ala Ser Gly Tyr Ser Gly Lys Ile Gln
Tyr Ser Asn His His Ile Lys Ala Ser Gly Tyr Ser Gly Lys Ile Gln
    775                 780                 785

acg gaa ggc aaa tgt tat agt acg aca tta ggg gcg gct ctc tct tgc   2515
Thr Glu Gly Lys Cys Tyr Ser Thr Thr Leu Gly Ala Ala Leu Ser Cys
Thr Glu Gly Lys Cys Tyr Ser Thr Thr Leu Gly Ala Ala Leu Ser Cys
790                 795                 800                 805

tct cta tct cta caa tgg cga tca cga cct ctc cac ttc act cct ttt   2563
Ser Leu Ser Leu Gln Trp Arg Ser Arg Pro Leu His Phe Thr Pro Phe
Ser Leu Ser Leu Gln Trp Arg Ser Arg Pro Leu His Phe Thr Pro Phe
                810                 815                 820

atc caa gca att gcc gtt cgt tct aat caa act gcg ttt caa gaa agt   2611
Ile Gln Ala Ile Ala Val Arg Ser Asn Gln Thr Ala Phe Gln Glu Ser
Ile Gln Ala Ile Ala Val Arg Ser Asn Gln Thr Ala Phe Gln Glu Ser
            825                 830                 835

gga gat aaa gct aga aaa ttt tct gtt cat aaa ccc tta tat aac ctg   2659
Gly Asp Lys Ala Arg Lys Phe Ser Val His Lys Pro Leu Tyr Asn Leu
Gly Asp Lys Ala Arg Lys Phe Ser Val His Lys Pro Leu Tyr Asn Leu
        840                 845                 850

aca gtc cct ctg gga att cag agc gct tgg gaa tcc aag ttc cgt ctt   2707
Thr Val Pro Leu Gly Ile Gln Ser Ala Trp Glu Ser Lys Phe Arg Leu
Thr Val Pro Leu Gly Ile Gln Ser Ala Trp Glu Ser Lys Phe Arg Leu
    855                 860                 865

cct acc tat tgg aac ata gag ctt gct tat cag cct gtc ctc tac caa   2755
Pro Thr Tyr Trp Asn Ile Glu Leu Ala Tyr Gln Pro Val Leu Tyr Gln
Pro Thr Tyr Trp Asn Ile Glu Leu Ala Tyr Gln Pro Val Leu Tyr Gln
870                 875                 880                 885

caa aat cct gag atc aac gtg agt cta gaa tct agt gga tcg tca tgg   2803
Gln Asn Pro Glu Ile Asn Val Ser Leu Glu Ser Ser Gly Ser Ser Trp
Gln Asn Pro Glu Ile Asn Val Ser Leu Glu Ser Ser Gly Ser Ser Trp
                890                 895                 900

ctc cta tca gga acc acc ctt gct cgc aat gcc att gct ttt aaa gga   2851
Leu Leu Ser Gly Thr Thr Leu Ala Arg Asn Ala Ile Ala Phe Lys Gly
Leu Leu Ser Gly Thr Thr Leu Ala Arg Asn Ala Ile Ala Phe Lys Gly
            905                 910                 915

aga aac caa att ttt atc ttc cct aaa ctt tcg gtg ttc tta gac tat   2899
Arg Asn Gln Ile Phe Ile Phe Pro Lys Leu Ser Val Phe Leu Asp Tyr
Arg Asn Gln Ile Phe Ile Phe Pro Lys Leu Ser Val Phe Leu Asp Tyr
        920                 925                 930

caa ggc tcg gta tcc tca tca acg acg aca cat tac ctt cac gca gga   2947
Gln Gly Ser Val Ser Ser Ser Thr Thr Thr His Tyr Leu His Ala Gly
Gln Gly Ser Val Ser Ser Ser Thr Thr Thr His Tyr Leu His Ala Gly
    935                 940                 945

acg acc ttt aag ttt taaaagcatg ttatatagac aatgcaacct gtaaagacca   3002
Thr Thr Phe Lys Phe
Thr Thr Phe Lys Phe
950

aatagagagt agtgaacact ctctaccatc atgaatctta tgggagaagc taagggaaat 3062

ccacagatac gtttcccccа taaaaattaa gaacccgata catcctcact agagattcga 3122

aagaactact taaatcctaa gcattcga                                    3150
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Fig. 19 (con't)

```
gtc aca gct aaa cat att aat acg gat aat ttc tac cct gag ggt cta   1891
Val Thr Ala Lys His Ile Asn Thr Asp Asn Phe Tyr Pro Glu Gly Leu
Val Thr Ala Lys His Ile Asn Thr Asp Asn Phe Tyr Pro Glu Gly Leu
            585                 590                 595

aat aca act caa cac tac ggc tac caa ggc gtt tgg tcc cct tac tgg   1939
Asn Thr Thr Gln His Tyr Gly Tyr Gln Gly Val Trp Ser Pro Tyr Trp
Asn Thr Thr Gln His Tyr Gly Tyr Gln Gly Val Trp Ser Pro Tyr Trp
        600                 605                 610

atc gaa aca atc aca act tct gat acc tct tct gaa gat act gtg aat   1987
Ile Glu Thr Ile Thr Thr Ser Asp Thr Ser Ser Glu Asp Thr Val Asn
Ile Glu Thr Ile Thr Thr Ser Asp Thr Ser Ser Glu Asp Thr Val Asn
    615                 620                 625

act tta cat cgc cag ctt tat ggt gat tgg aca cct aca gga tat aag   2035
Thr Leu His Arg Gln Leu Tyr Gly Asp Trp Thr Pro Thr Gly Tyr Lys
Thr Leu His Arg Gln Leu Tyr Gly Asp Trp Thr Pro Thr Gly Tyr Lys
630                 635                 640                 645

gta aac cca gaa aac aaa gga gac att gcc cta tct gcc ttc tgg caa   2083
Val Asn Pro Glu Asn Lys Gly Asp Ile Ala Leu Ser Ala Phe Trp Gln
Val Asn Pro Glu Asn Lys Gly Asp Ile Ala Leu Ser Ala Phe Trp Gln
                650                 655                 660

tct ttc cat aac tta ttt gcg aca cta cgt tat caa aca cag caa ggc   2131
Ser Phe His Asn Leu Phe Ala Thr Leu Arg Tyr Gln Thr Gln Gln Gly
Ser Phe His Asn Leu Phe Ala Thr Leu Arg Tyr Gln Thr Gln Gln Gly
            665                 670                 675

caa ata gca cct aca gct tct gga gaa gct act cga ctc ttc gtg cat   2179
Gln Ile Ala Pro Thr Ala Ser Gly Glu Ala Thr Arg Leu Phe Val His
Gln Ile Ala Pro Thr Ala Ser Gly Glu Ala Thr Arg Leu Phe Val His
        680                 685                 690

caa aat agc aac aat gat gcg aaa gga ttc cat atg gaa gct acg ggt   2227
Gln Asn Ser Asn Asn Asp Ala Lys Gly Phe His Met Glu Ala Thr Gly
Gln Asn Ser Asn Asn Asp Ala Lys Gly Phe His Met Glu Ala Thr Gly
    695                 700                 705

tat tct ttg gga aca acc tca aac act gct tct aat cat agc ttt ggt   2275
Tyr Ser Leu Gly Thr Thr Ser Asn Thr Ala Ser Asn His Ser Phe Gly
Tyr Ser Leu Gly Thr Thr Ser Asn Thr Ala Ser Asn His Ser Phe Gly
710                 715                 720                 725

gta aac ttc tcc caa ctt ttc agt aat ctc tac gag agc cac tcc gac   2323
Val Asn Phe Ser Gln Leu Phe Ser Asn Leu Tyr Glu Ser His Ser Asp
Val Asn Phe Ser Gln Leu Phe Ser Asn Leu Tyr Glu Ser His Ser Asp
                730                 735                 740

aat tcc gtg gct tcg cat acg aca act gta gcg ctc cag atc aat aat   2371
Asn Ser Val Ala Ser His Thr Thr Thr Val Ala Leu Gln Ile Asn Asn
Asn Ser Val Ala Ser His Thr Thr Thr Val Ala Leu Gln Ile Asn Asn
            745                 750                 755

cct tgg ctg caa gag aga ttc tct aca tct gca tct cta gcc tac agc   2419
Pro Trp Leu Gln Glu Arg Phe Ser Thr Ser Ala Ser Leu Ala Tyr Ser
Pro Trp Leu Gln Glu Arg Phe Ser Thr Ser Ala Ser Leu Ala Tyr Ser
        760                 765                 770
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Figure 20 (RY-44)

Restriction enzyme analysis of CPN100622

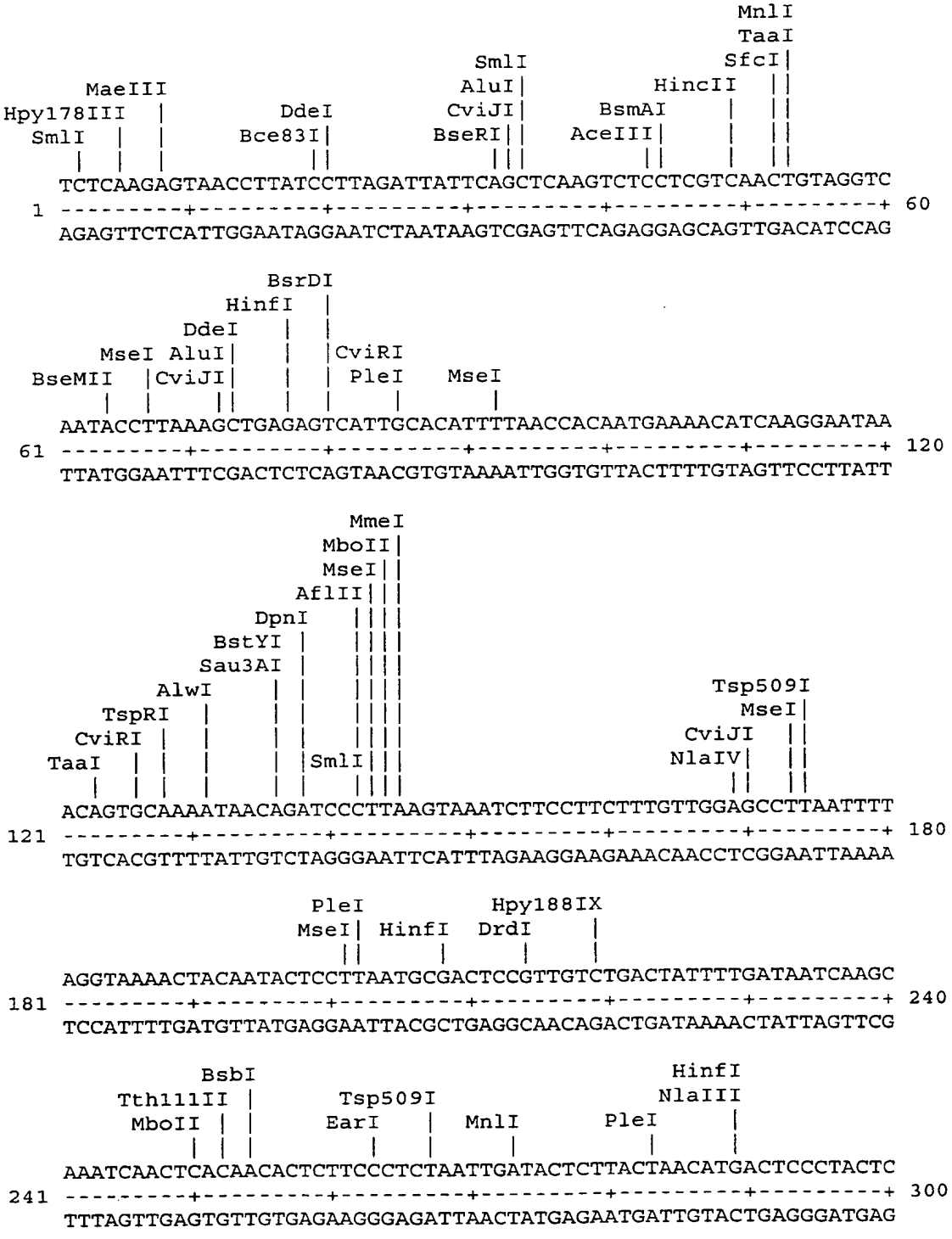
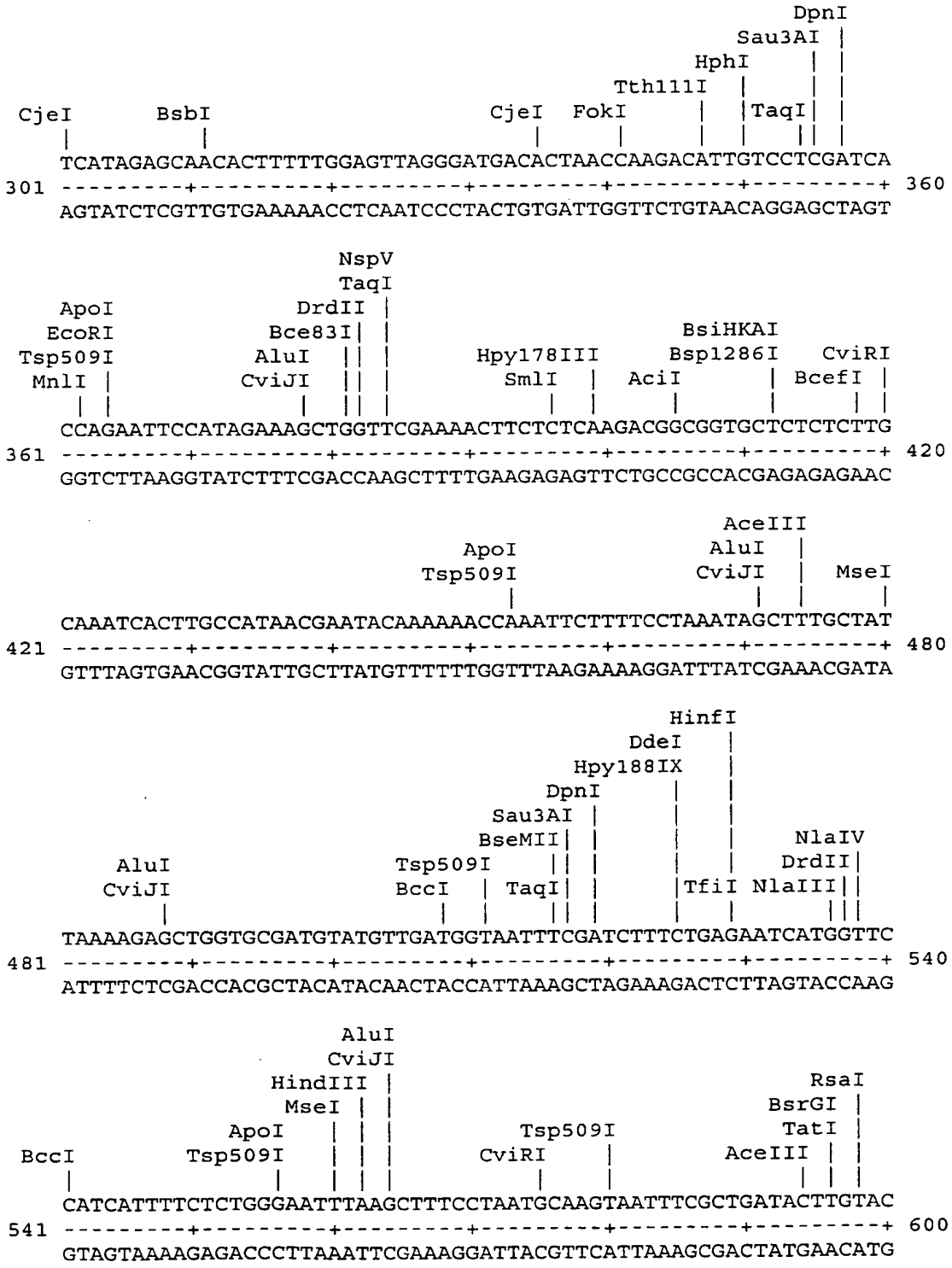


Fig. 20 (con't)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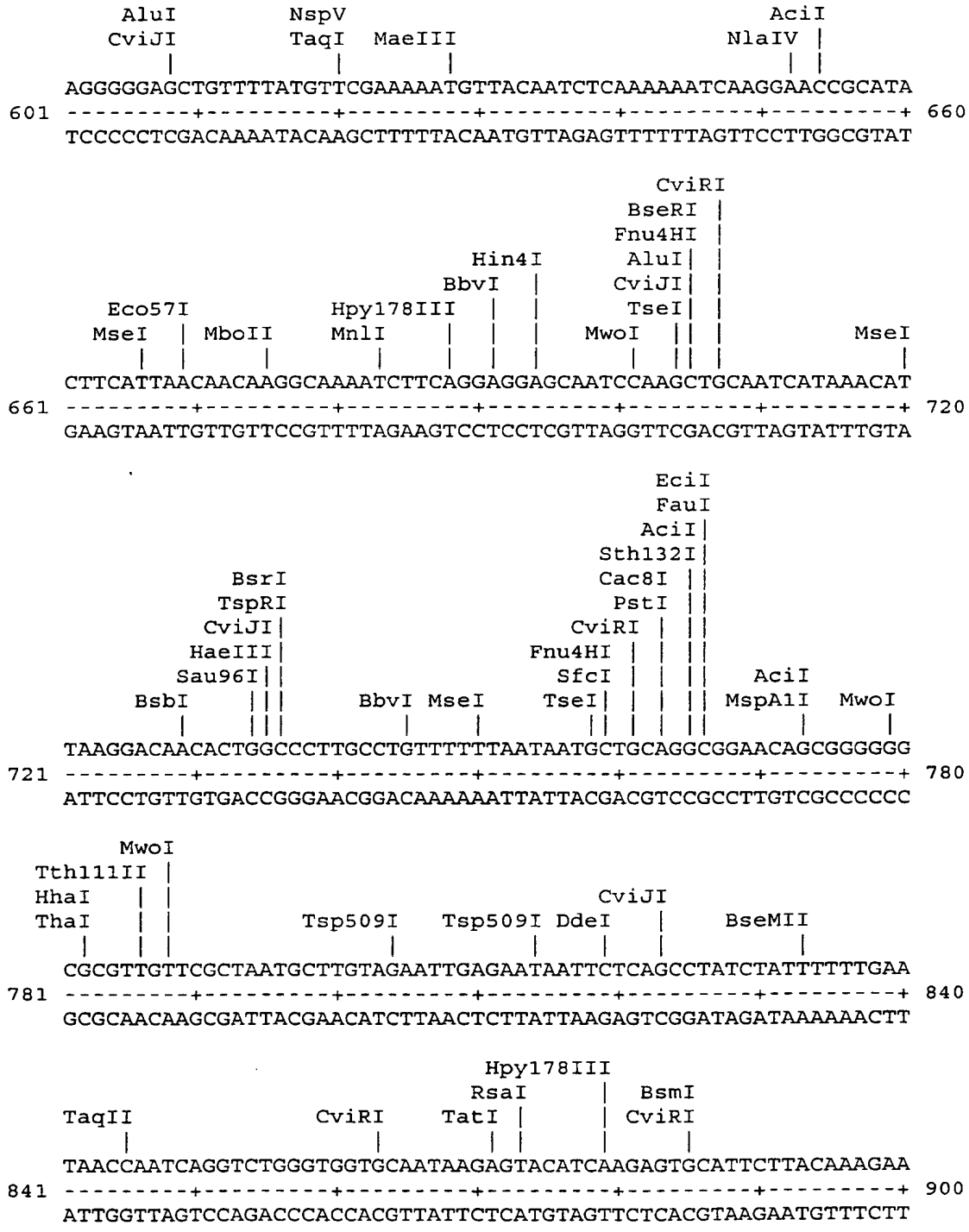
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Fig. 20 (con't)

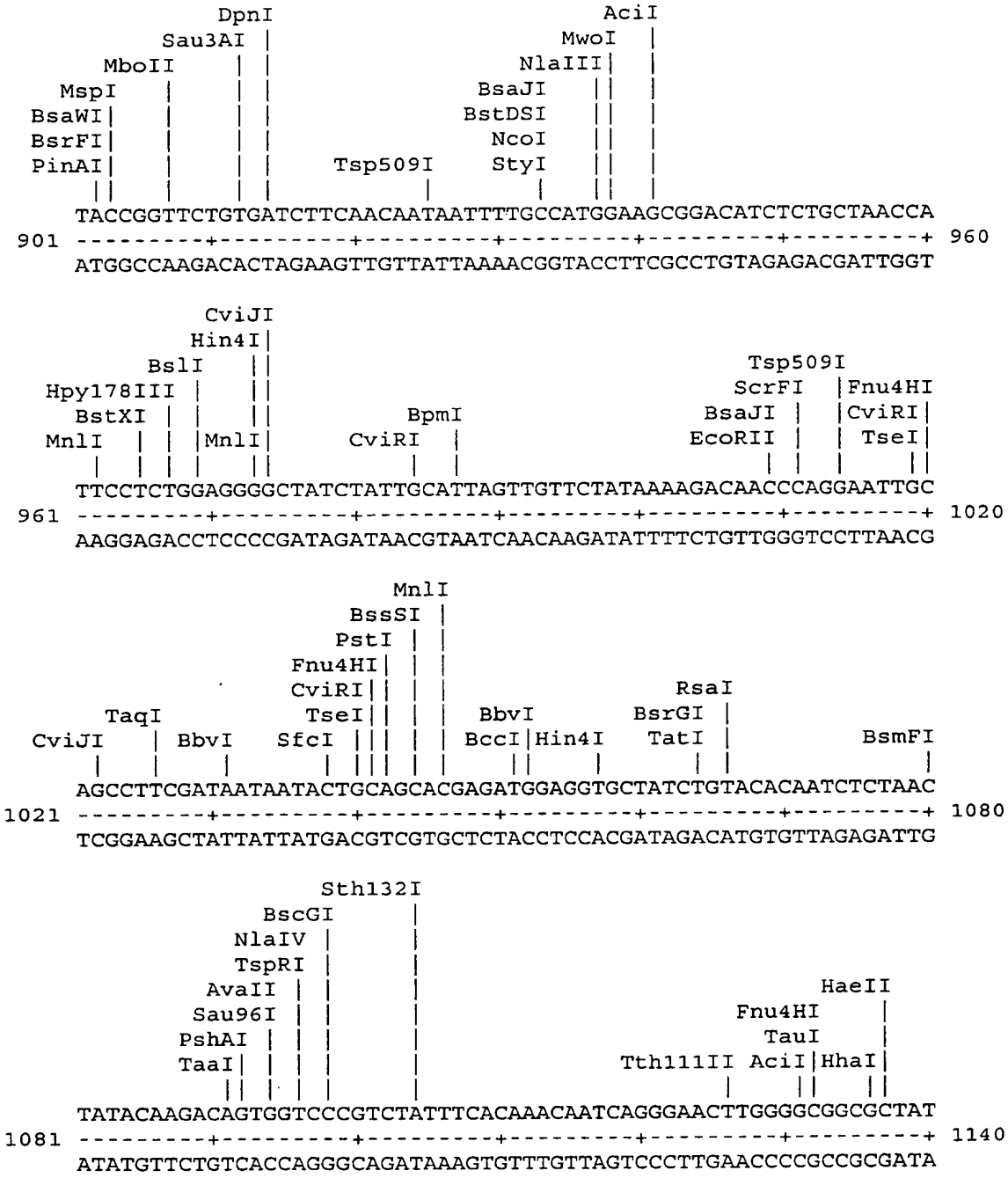
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Fig. 20 (con't)

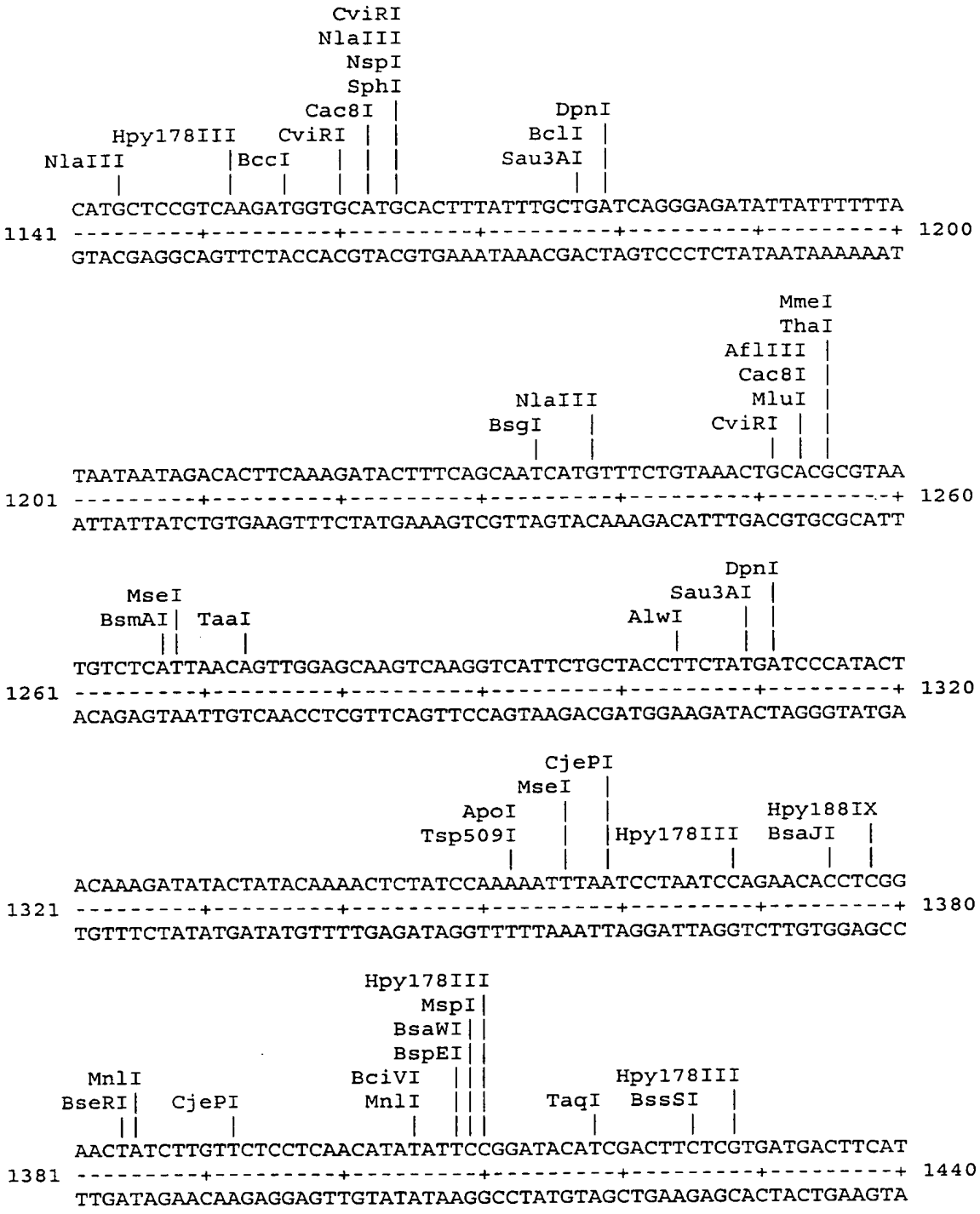
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Fig. 20 (con't)

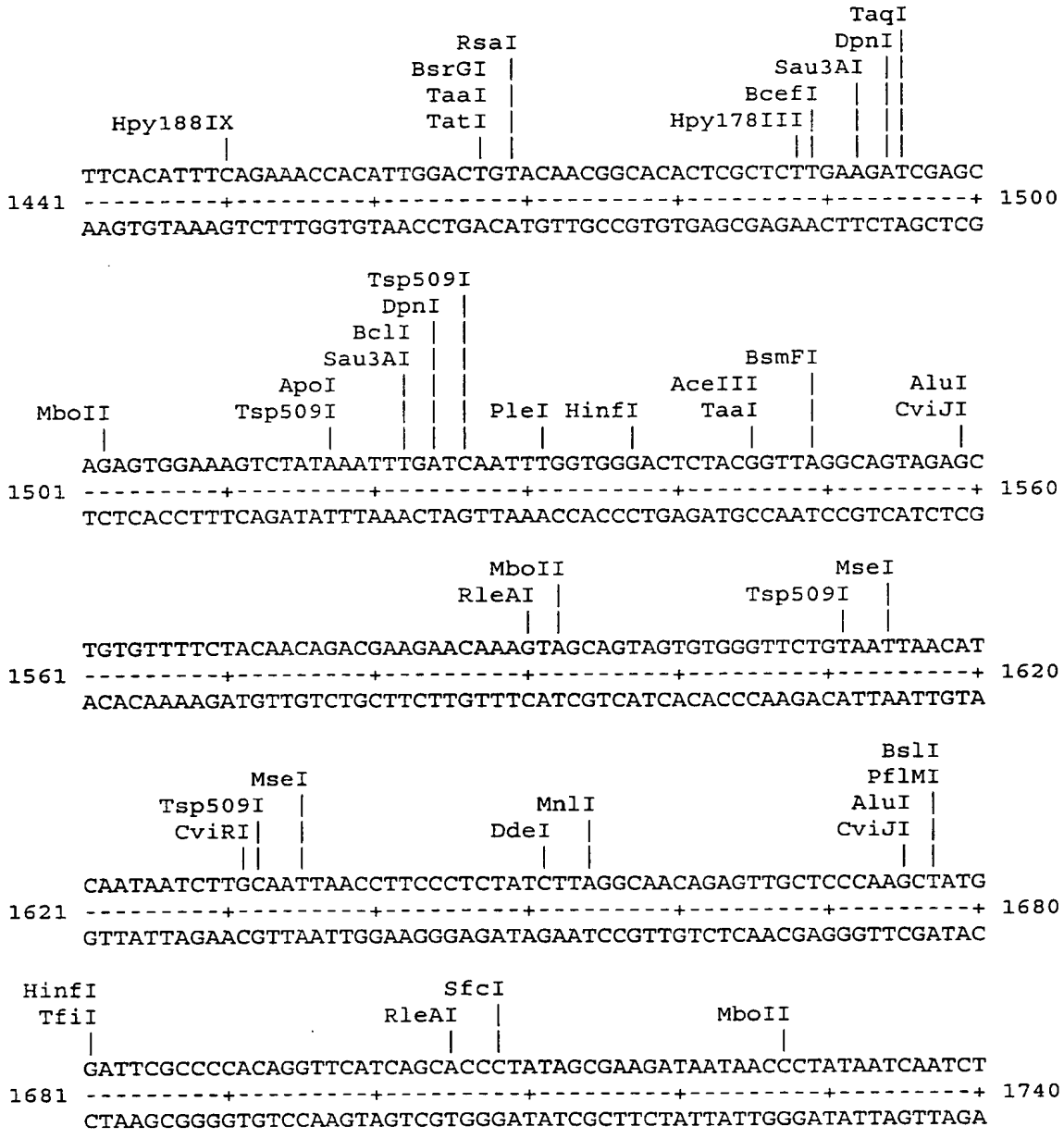
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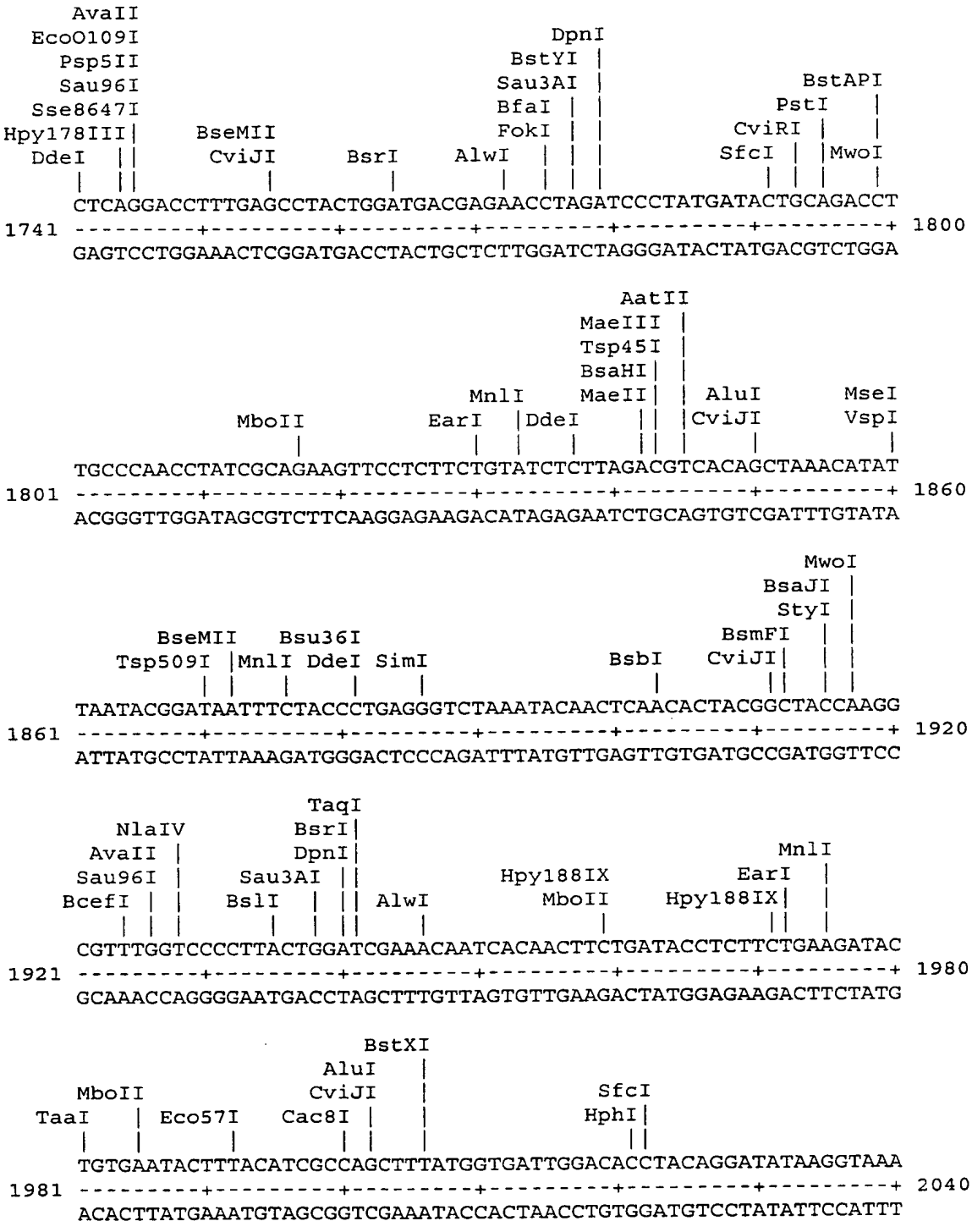
Fig. 20 (con't)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MaeIII
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MnlI
MaeII
MboII
EarI
DdeI
AluI
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VspI
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BsaJI
StyI
BseMII
Tsp509I
Bsu36I
MnlI
DdeI
SimI
BsmFI
BsbI
CviJI
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1920
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BsrI
AvaII
DpnI
Sau96I
Sau3AI
BcefI
BslI
AlwI
Hpy188IX
MboII
MnlI
EarI
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SfcI
TaaI
Eco57I
Cac8I
HphI
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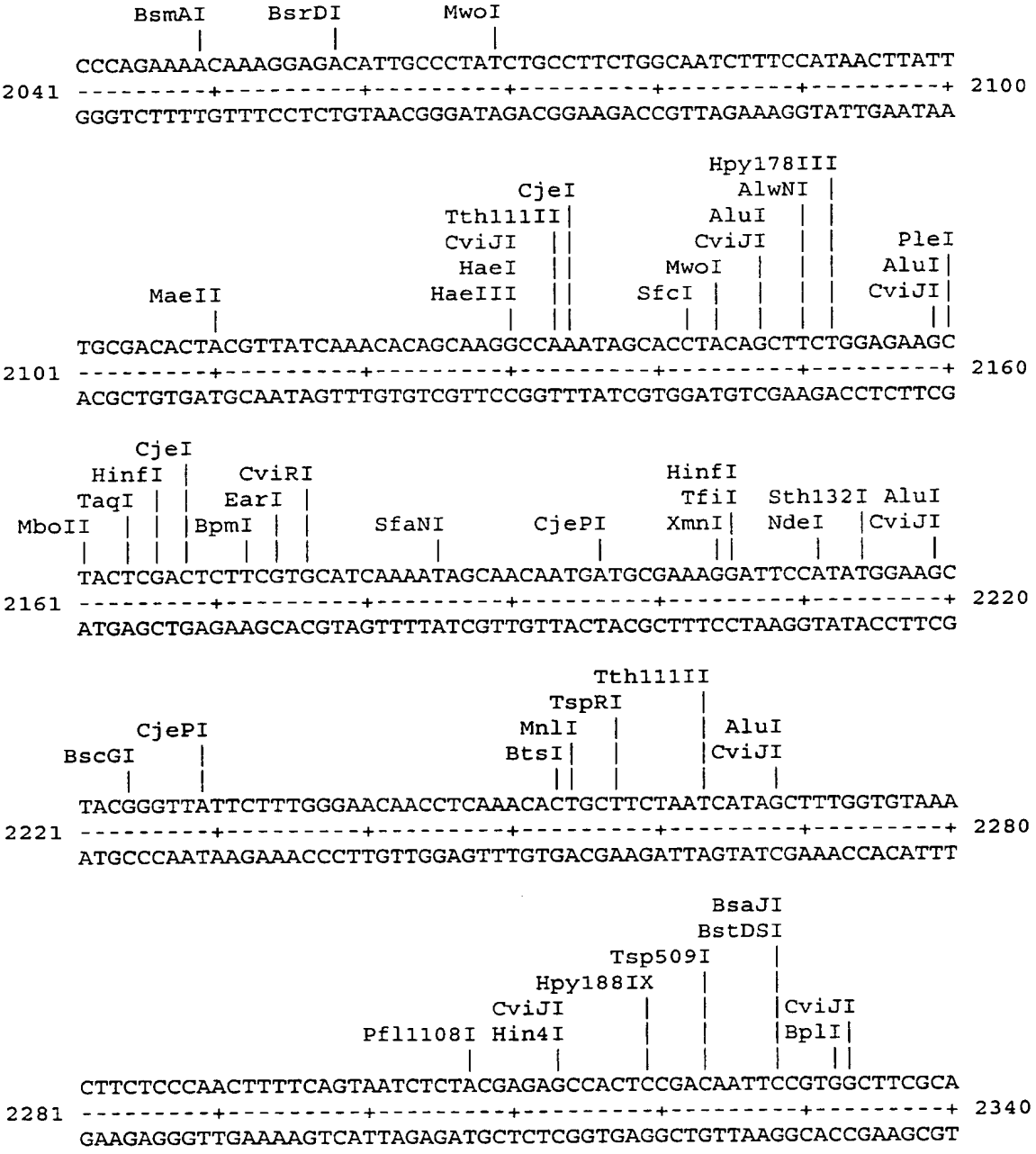
Fig. 20 (con't)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CviJI
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MwoI
PleI
AluI
MaeII
HaeIII
SfcI
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HinfI
CviRI
HinfI
TaqI
EarI
TfiI
Sth132I
AluI
MboII
BpmI
SfaNI
CjePI
XmnI
NdeI
CviJI
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2161
2220
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Tth111II
TspRI
CjePI
MnlI
AluI
BscGI
BtsI
CviJI
TACGGGTTATTCTTTGGGAACAACCTCAAACACTGCTTCTAATCATAGCTTTGGTGTAAA
2221
2280
ATGCCCAATAAGAAACCCTTGTTGGAGTTTGTGACGAAGATTAGTATCGAAACCACATTT
BsaJI
BstDSI
Tsp509I
Hpy188IX
CviJI
CviJI
Pfl1108I
Hin4I
BplI
CTTCTCCCAACTTTTCAGTAATCTCTACGAGAGCCACTCCGACAATTCCGTGGCTTCGCA
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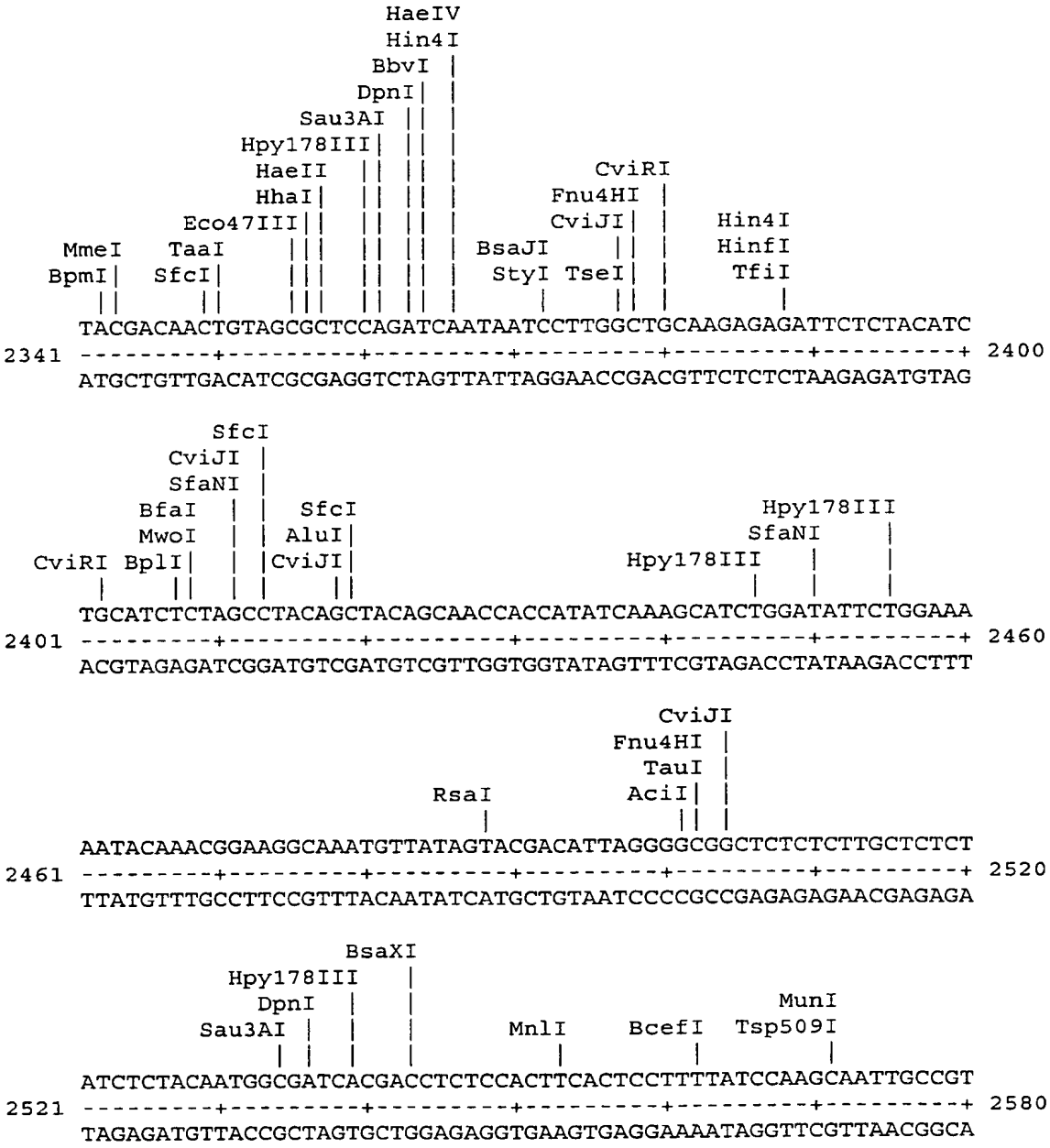
Fig. 20 (con't)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Fnu4HI
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SfcI
AluI
CviJI
Hpy178III
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Fnu4HI
TauI
RsaI
AciI
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Hpy178III
DpnI
Sau3AI
MnlI
BcefI
MunI
Tsp509I
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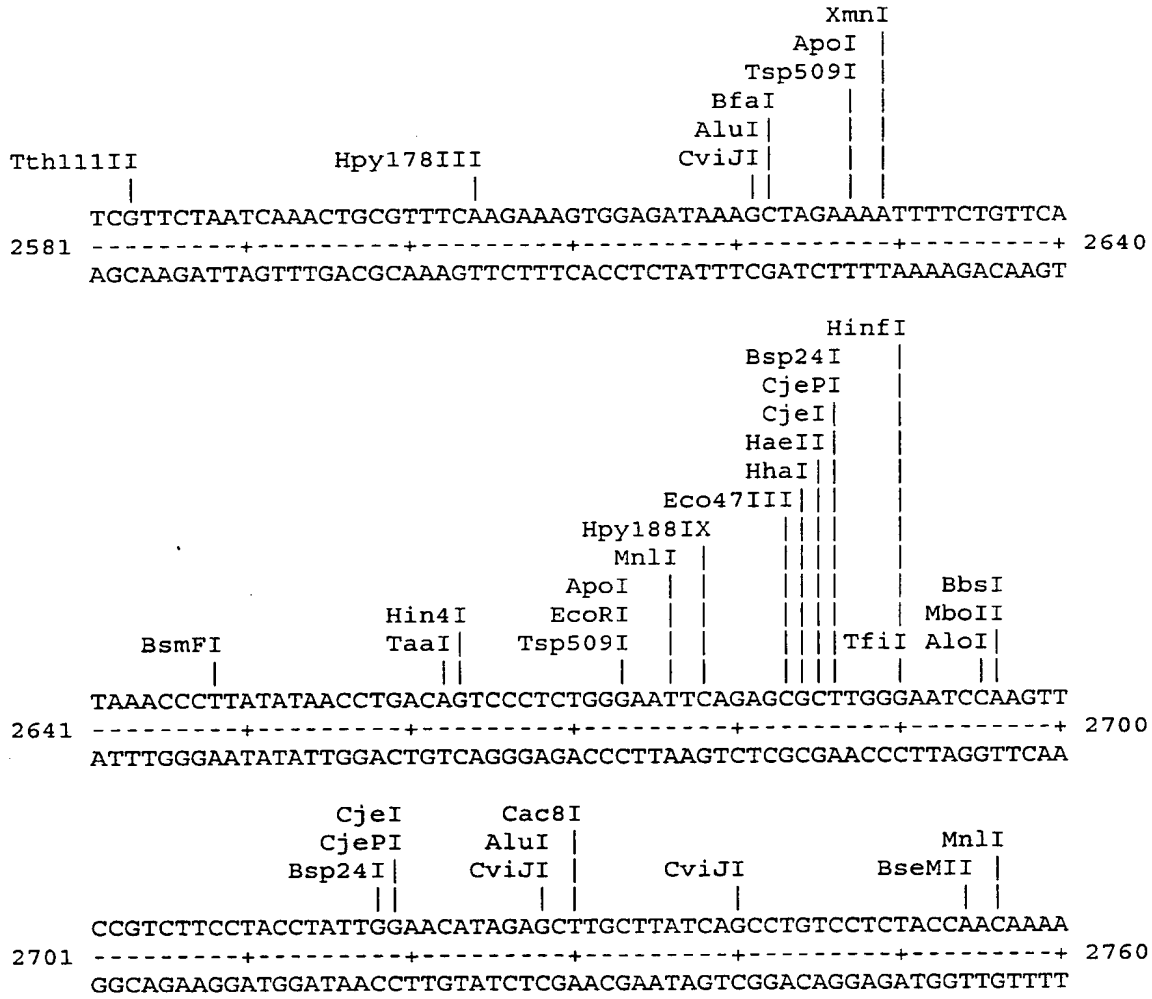
Fig. 20 (con't)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CjeI
HaeII
HhaI
Eco47III
Hpy188IX
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ApoI
EcoRI
Tsp509I
Hin4I
TaaI
BsmFI
TfiI
BbsI
MboII
AloI
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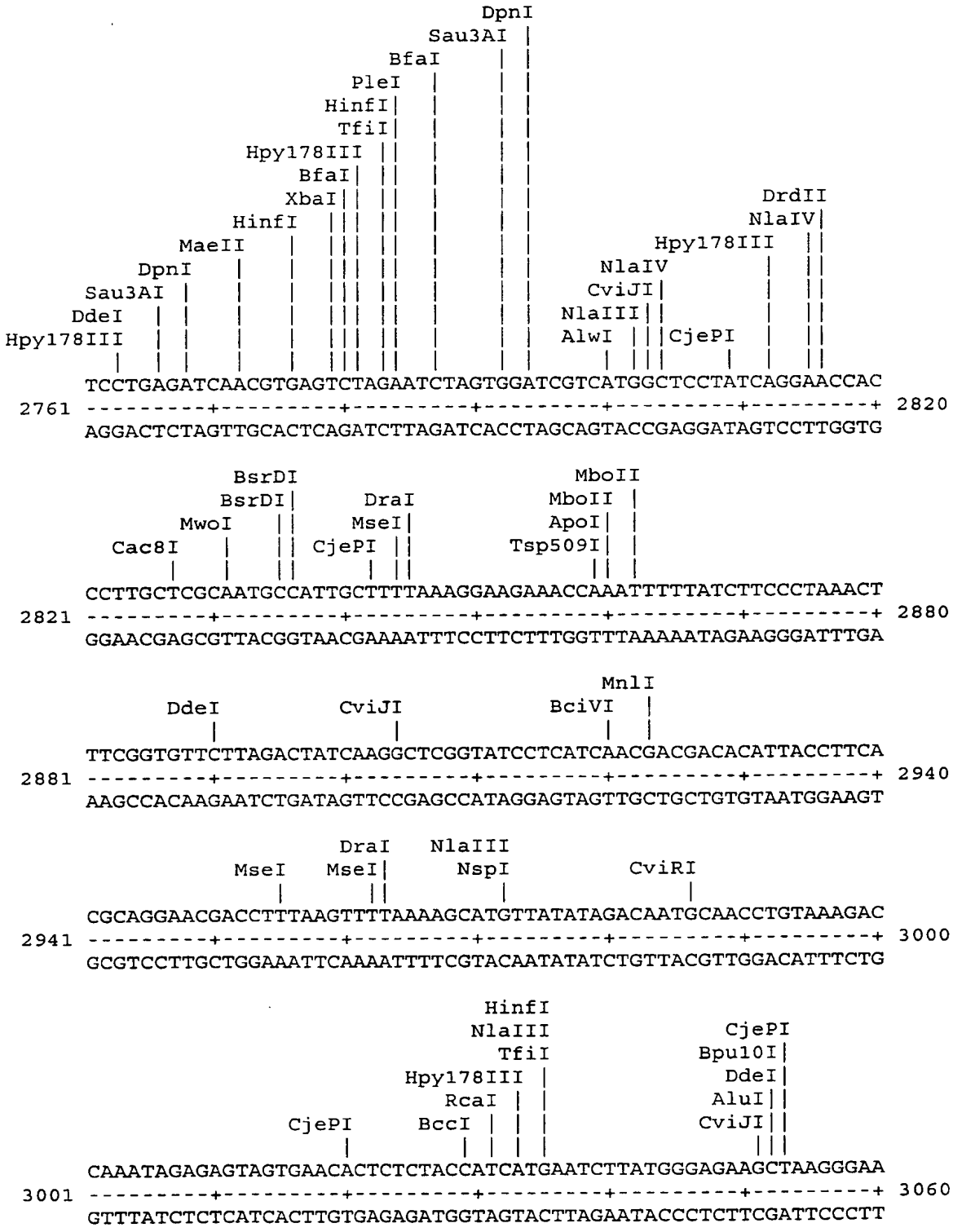
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DdeI
Hpy178III
DrdII
NlaIV
Hpy178III
NlaIV
CviJI
NlaIII
AlwI
CjePI
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BsrDI
BsrDI
MwoI
Cac8I
DraI
MseI
CjePI
MboII
MboII
ApoI
Tsp509I
CCTTGCTCGCAATGCCATTGCTTTTAAAGGAAGAAACCAAATTTTTATCTTCCCTAAACT
2821 ---------+---------+---------+---------+---------+---------+ 2880
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MnlI
DdeI
CviJI
BciVI
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DraI
NlaIII
MseI
MseI
NspI
CviRI
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2941 ---------+---------+---------+---------+---------+---------+ 3000
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Bpu10I
DdeI
AluI
CviJI
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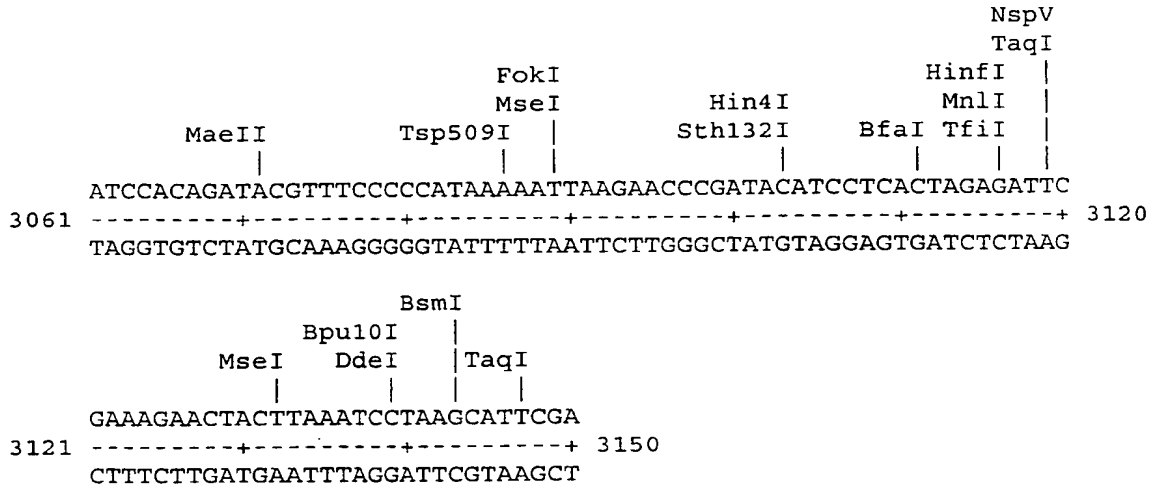
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MseI
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3120
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BsmI
Bpu10I
MseI
DdeI
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3150
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Figure 21A: CPN100626 Coding Sequence

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```

Figure 21B: CPN100626 Deduced Amino Acid Sequence

```
Met Gln Val Phe Pro Lys Val Thr Leu Ser Leu Asp Tyr Ser Ala Asp
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Ile Ser Ser Ser Thr Leu Ser His Tyr Leu Asn Val Ala Ser Arg Met
            20                  25                  30

Arg Phe Leu Thr Ile Ser Asp Gln Asn Arg Lys Ile Lys Glu Pro Leu
        35                  40                  45

Val Ser Lys Thr Pro Pro Lys Phe Leu Phe Tyr Leu Gly Asn Phe Thr
    50                  55                  60

Ala Cys Met Phe Gly Met Thr Pro Ala Val Tyr Ser Leu Gln Thr Asp
65                  70                  75                  80

Ser Leu Glu Lys Phe Ala Leu Glu Arg Asp Glu Glu Phe Arg Thr Ser
                85                  90                  95

Phe Pro Leu Leu Asp Ser Leu Ser Thr Leu Thr Gly Phe Ser Pro Ile
            100                 105                 110

Thr Thr Phe Val Gly Asn Arg His Asn Ser Ser Gln Asp Ile Val Leu
        115                 120                 125

Ser Asn Tyr Lys Ser Ile Asp Asn Ile Leu Leu Leu Trp Thr Ser Ala
    130                 135                 140

Gly Gly Ala Val Ser Cys Asn Asn Phe Leu Leu Ser Asn Val Glu Asp
145                 150                 155                 160

His Ala Phe Phe Ser Lys Asn Leu Ala Ile Gly Thr Gly Gly Ala Ile
                165                 170                 175

Ala Cys Gln Gly Ala Cys Thr Ile Thr Lys Asn Arg Gly Pro Leu Ile
            180                 185                 190

Phe Phe Ser Asn Arg Gly Leu Asn Asn Ala Ser Thr Gly Gly Glu Thr
        195                 200                 205

Arg Gly Gly Ala Ile Ala Cys Asn Gly Asp Phe Thr Ile Ser Gln Asn
    210                 215                 220

Gln Gly Thr Phe Tyr Phe Val Asn Asn Ser Val Asn Asn Trp Gly Gly
225                 230                 235                 240

Ala Leu Ser Thr Asn Gly His Cys Arg Ile Gln Ser Asn Arg Ala Pro
                245                 250                 255

Leu Leu Phe Phe Asn Asn Thr Ala Pro Ser Gly Gly Gly Ala Leu Arg
            260                 265                 270

Ser Glu Asn Thr Thr Ile Ser Asp Asn Thr Arg Pro Ile Tyr Phe Lys
        275                 280                 285
```

Fig. 21B (con't)

```
Asn Asn Cys Gly Asn Asn Gly Gly Ala Ile Gln Thr Ser Val Thr Val
    290                 295                 300

Ala Ile Lys Asn Asn Ser Gly Ser Val Ile Phe Asn Asn Asn Thr Ala
305                 310                 315                 320

Leu Ser Gly Ser Ile Asn Ser Gly Asn Gly Ser Gly Gly Ala Ile Tyr
                325                 330                 335

Thr Thr Asn Leu Ser Ile Asp Asp Asn Pro Gly Thr Ile Leu Phe Asn
            340                 345                 350

Asn Asn Tyr Cys Ile Arg Asp Gly Gly Ala Ile Cys Thr Gln Phe Leu
        355                 360                 365

Thr Ile Lys Asn Ser Gly His Val Tyr Phe Thr Asn Asn Gln Gly Asn
    370                 375                 380

Trp Gly Gly Ala Leu Met Leu Leu Gln Asp Ser Thr Cys Leu Leu Phe
385                 390                 395                 400

Ala Glu Gln Gly Asn Ile Ala Phe Gln Asn Asn Glu Val Phe Leu Thr
                405                 410                 415

Thr Phe Gly Arg Tyr Asn Ala Ile His Cys Thr Pro Asn Ser Asn Leu
            420                 425                 430

Gln Leu Gly Ala Asn Lys Gly Tyr Thr Thr Ala Phe Phe Asp Pro Ile
        435                 440                 445

Glu His Gln His Pro Thr Thr Asn Pro Leu Ile Phe Asn Pro Asn Ala
    450                 455                 460

Asn His Gln Gly Thr Ile Leu Phe Ser Ser Ala Tyr Ile Pro Glu Ala
465                 470                 475                 480

Ser Asp Tyr Glu Asn Asn Phe Ile Ser Ser Ser Lys Asn Thr Ser Glu
                485                 490                 495

Leu Arg Asn Gly Val Leu Ser Ile Glu Asp Arg Ala Gly Trp Gln Phe
            500                 505                 510

Tyr Lys Phe Thr Gln Lys Gly Gly Ile Leu Lys Leu Gly His Ala Ala
        515                 520                 525

Ser Ile Ala Thr Thr Ala Asn Ser Glu Thr Pro Ser Thr Ser Val Gly
    530                 535                 540

Ser Gln Val Ile Ile Asn Asn Leu Ala Ile Asn Leu Pro Ser Ile Leu
545                 550                 555                 560

Ala Lys Gly Lys Ala Pro Thr Leu Trp Ile Arg Pro Leu Gln Ser Ser
                565                 570                 575
```

Fig. 21B (con't)

```
Ala Pro Phe Thr Glu Asp Asn Asn Pro Thr Ile Thr Leu Ser Gly Pro
            580                 585                 590

Leu Thr Leu Leu Asn Glu Glu Asn Arg Asp Pro Tyr Asp Ser Ile Asp
        595                 600                 605

Leu Ser Glu Pro Leu Gln Asn Ile His Leu Leu Ser Leu Ser Asp Val
    610                 615                 620

Thr Ala Arg His Ile Asn Thr Asp Asn Phe His Pro Glu Ser Leu Asn
625                 630                 635                 640

Ala Thr Glu His Tyr Gly Tyr Gln Gly Ile Trp Ser Pro Tyr Trp Val
                645                 650                 655

Glu Thr Ile Thr Thr Thr Asn Asn Ala Ser Ile Glu Thr Ala Asn Thr
            660                 665                 670

Leu Tyr Arg Ala Leu Tyr Ala Asn Trp Thr Pro Leu Gly Tyr Lys Val
        675                 680                 685

Asn Pro Glu Tyr Gln Gly Asp Leu Ala Thr Thr Pro Leu Trp Gln Ser
    690                 695                 700

Phe His Thr Met Phe Ser Leu Leu Arg Ser Tyr Asn Arg Thr Gly Asp
705                 710                 715                 720

Ser Asp Ile Glu Arg Pro Phe Leu Glu Ile Gln Gly Ile Ala Asp Gly
                725                 730                 735

Leu Phe Val His Gln Asn Ser Ile Pro Gly Ala Pro Gly Phe Arg Ile
            740                 745                 750

Gln Ser Thr Gly Tyr Ser Leu Gln Ala Ser Ser Glu Thr Ser Leu His
        755                 760                 765

Gln Lys Ile Ser Leu Gly Phe Ala Gln Phe Phe Thr Arg Thr Lys Glu
    770                 775                 780

Ile Gly Ser Ser Asn Asn Val Ser Ala His Asn Thr Val Ser Ser Leu
785                 790                 795                 800

Tyr Val Glu Leu Pro Trp Phe Gln Glu Ala Phe Ala Thr Ser His Ser
                805                 810                 815

Leu Ala Tyr Gly Tyr Gly Asp His His Leu His Ala Tyr Ile Arg His
            820                 825                 830

Ile Lys Asn Arg Ala Glu Gly Thr Cys Tyr Ser His Thr Leu Ala Ala
        835                 840                 845

Ala Ile Gly Cys Ser Phe Pro Trp Gln Gln Lys Ser Tyr Leu His Leu
    850                 855                 860
```

Fig. 21B (con't)

```
Ser Pro Phe Val Gln Ala Ile Ala Ile Arg Ser His Gln Thr Ala Phe
865                 870                 875                 880

Glu Glu Ile Gly Asp Asn Pro Arg Lys Phe Val Ser Gln Lys Pro Phe
                885                 890                 895

Tyr Asn Leu Thr Leu Pro Leu Gly Ile Gln Gly Lys Trp Gln Ser Lys
            900                 905                 910

Phe His Val Pro Thr Glu Trp Thr Leu Glu Leu Ser Tyr Gln Pro Val
        915                 920                 925

Leu Tyr Gln Gln Asn Pro Gln Ile Gly Val Thr Leu Leu Ala Ser Gly
    930                 935                 940

Gly Ser Trp Asp Ile Leu Gly His Asn Tyr Val Arg Asn Ala Leu Gly
945                 950                 955                 960

Tyr Lys Val His Asn Gln Thr Ala Leu Phe Arg Ser Leu Asp Leu Phe
                965                 970                 975

Leu Asp Tyr Gln Gly Ser Val Ser Ser Ser Thr Ser Thr His His Leu
            980                 985                 990

Gln Ala Gly Ser Thr Leu Lys Phe
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Figure 22 (RY-45)

Restriction enzyme analysis of CPN100626

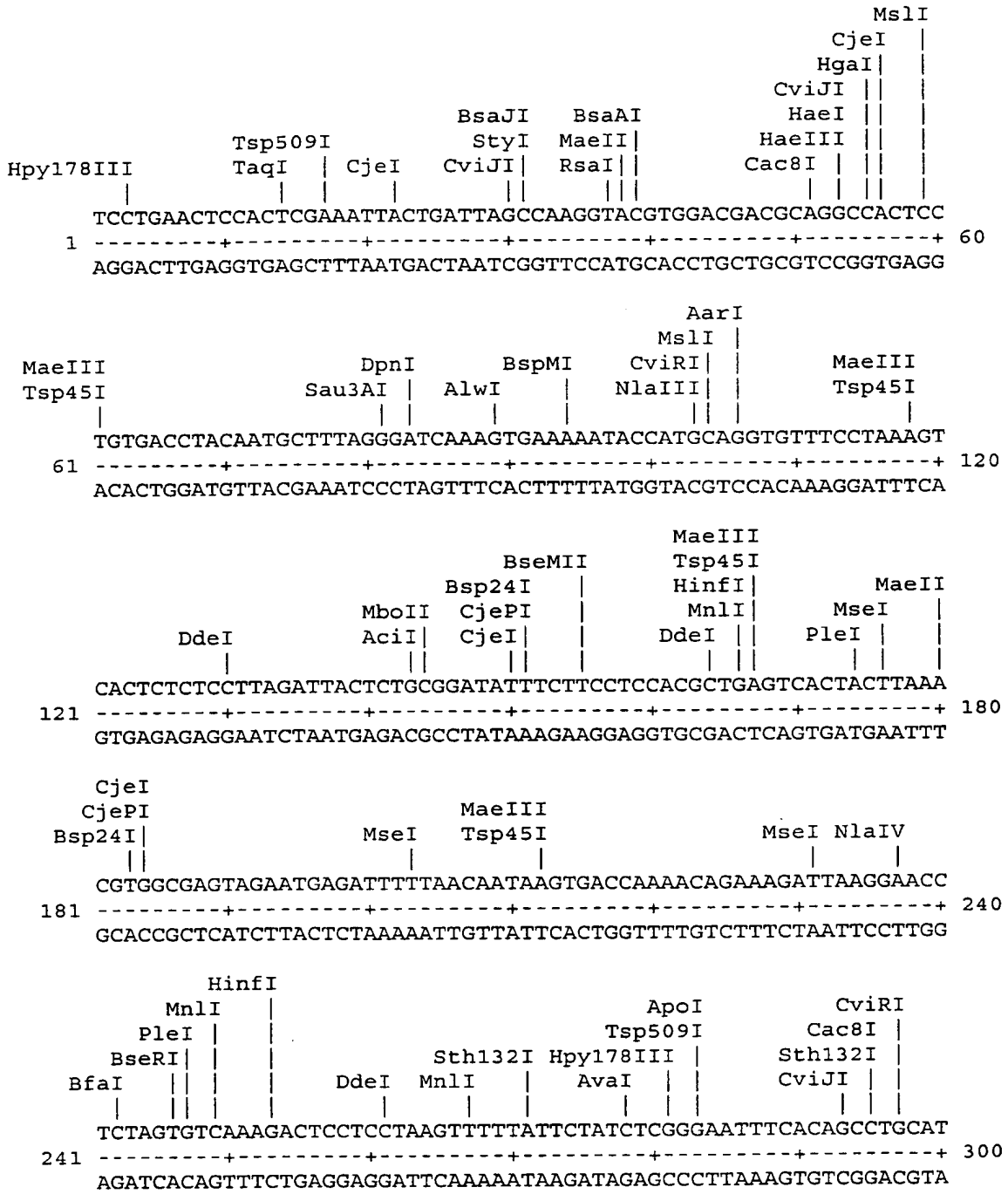
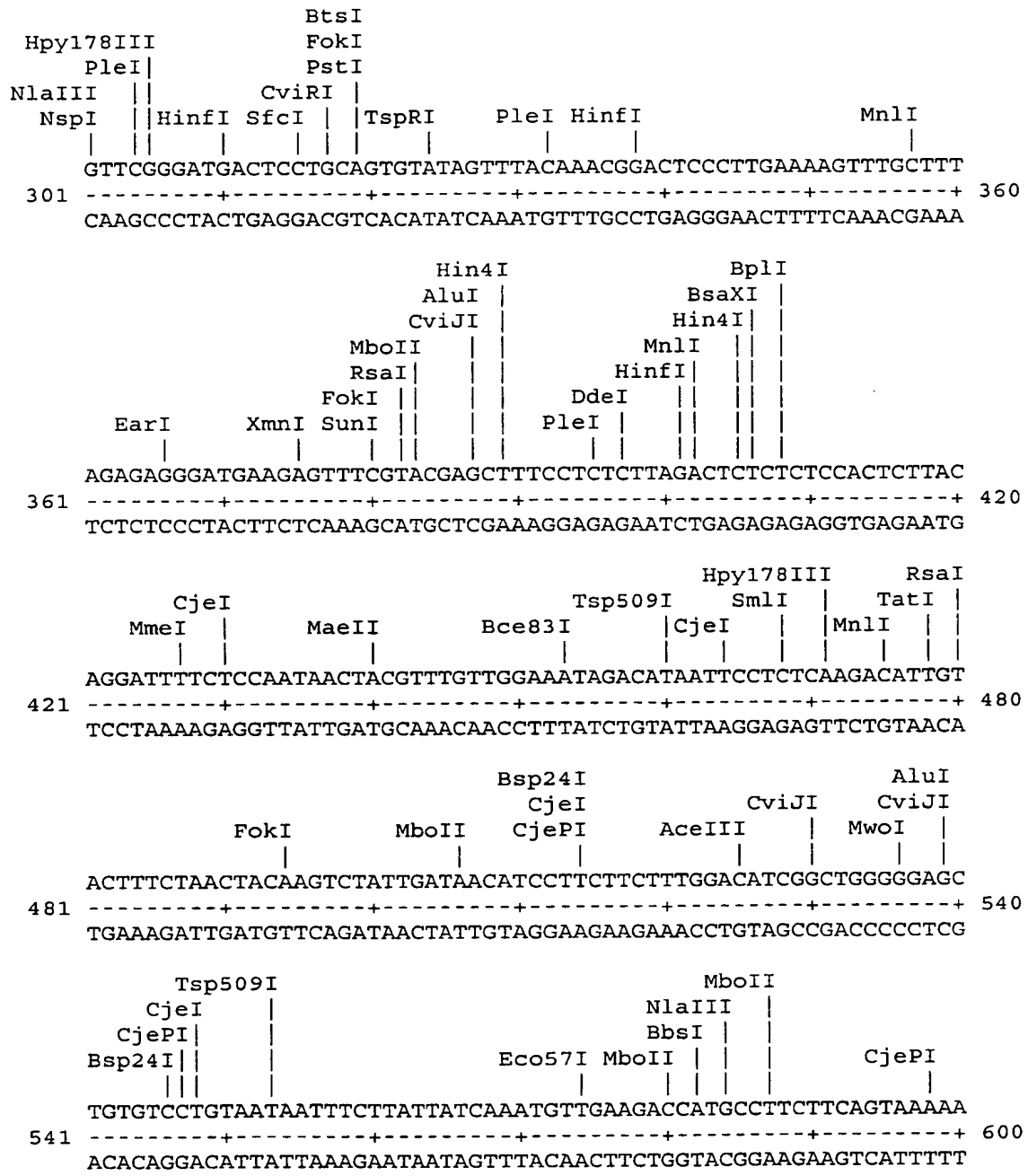


Fig. 22 (con't)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PleI| PstI
NlaIII || CviRI |
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301 360
CAAGCCCTACTGAGGACGTCACATATCAAATGTTTGCCTGAGGGAACTTTTCAAACGAAA
Hin4I BplI
AluI | BsaXI |
CviJI | Hin4I| |
MboII | | MnlI || |
RsaI| | | HinfI| || |
FokI || | | DdeI || || |
EarI XmnI SunI || | | PleI | || || |
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361 420
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Hpy178III RsaI
CjeI Tsp509I SmlI | TatI |
MmeI | MaeII Bce83I |CjeI | | |MnlI | | |
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421 480
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Bsp24I AluI
CjeI CviJI CviJI
FokI MboII CjePI AceIII | MwoI |
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481 540
TGAAAGATTGATGTTCAGATAACTATTGTAGGAAGAAGAAACCTGTAGCCGACCCCCTCG
Tsp509I MboII
CjeI NlaIII |
CjePI| BbsI | |
Bsp24I|| Eco57I MboII | | | CjePI
||| | | | | |
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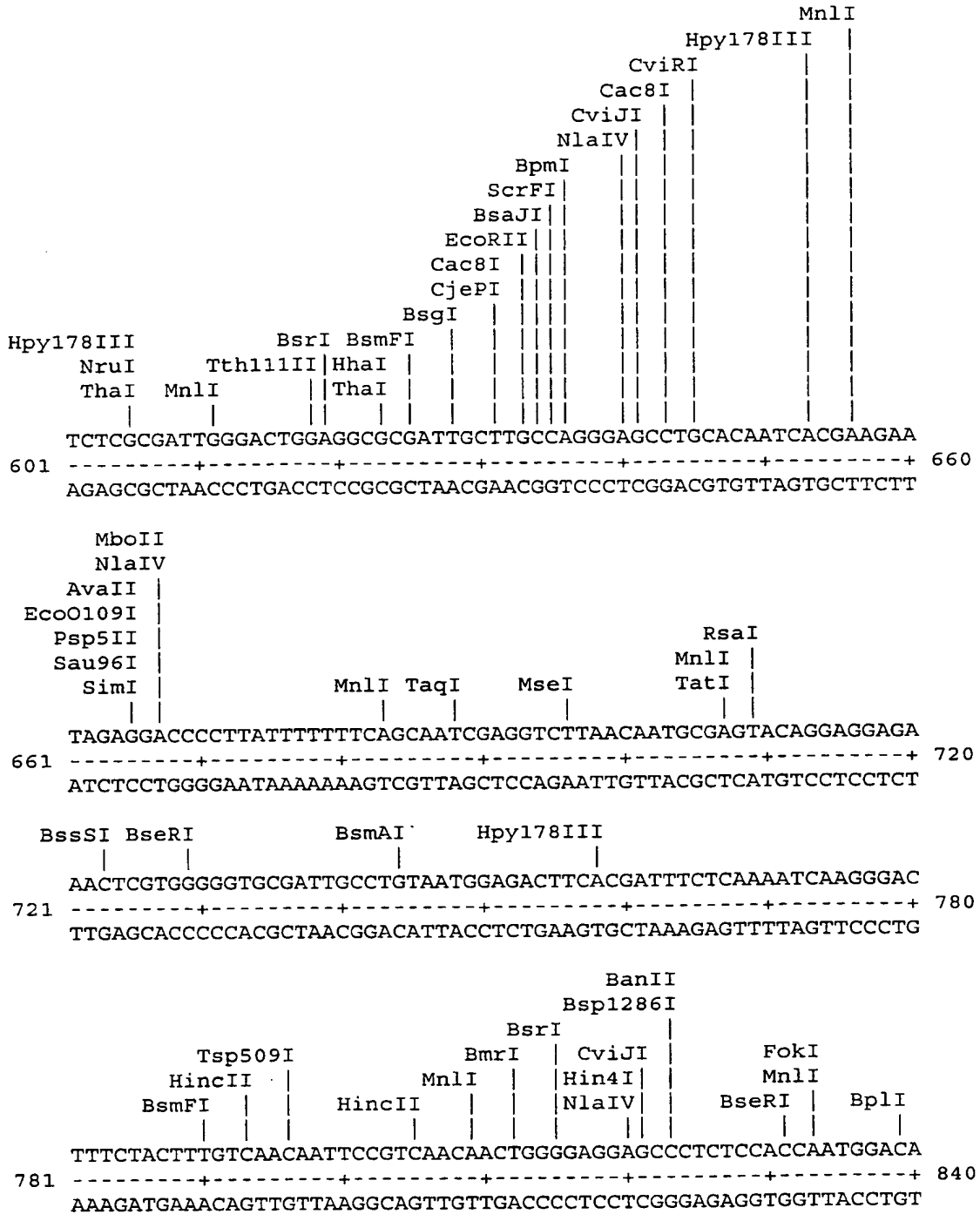
Fig. 22 (con't)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BsgI
Hpy178III
BsrI BsmFI
NruI
Tth111II
HhaI
ThaI
MnlI
ThaI
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NlaIV
AvaII
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Psp5II
Sau96I
SimI
RsaI
MnlI
TatI
MnlI TaqI
MseI
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BssSI BseRI
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721 ---------+---------+---------+---------+---------+---------+ 780
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Bsp1286I
BsrI
Tsp509I
BmrI
CviJI
FokI
HincII
MnlI
Hin4I
MnlI
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HincII
NlaIV
BseRI
BplI
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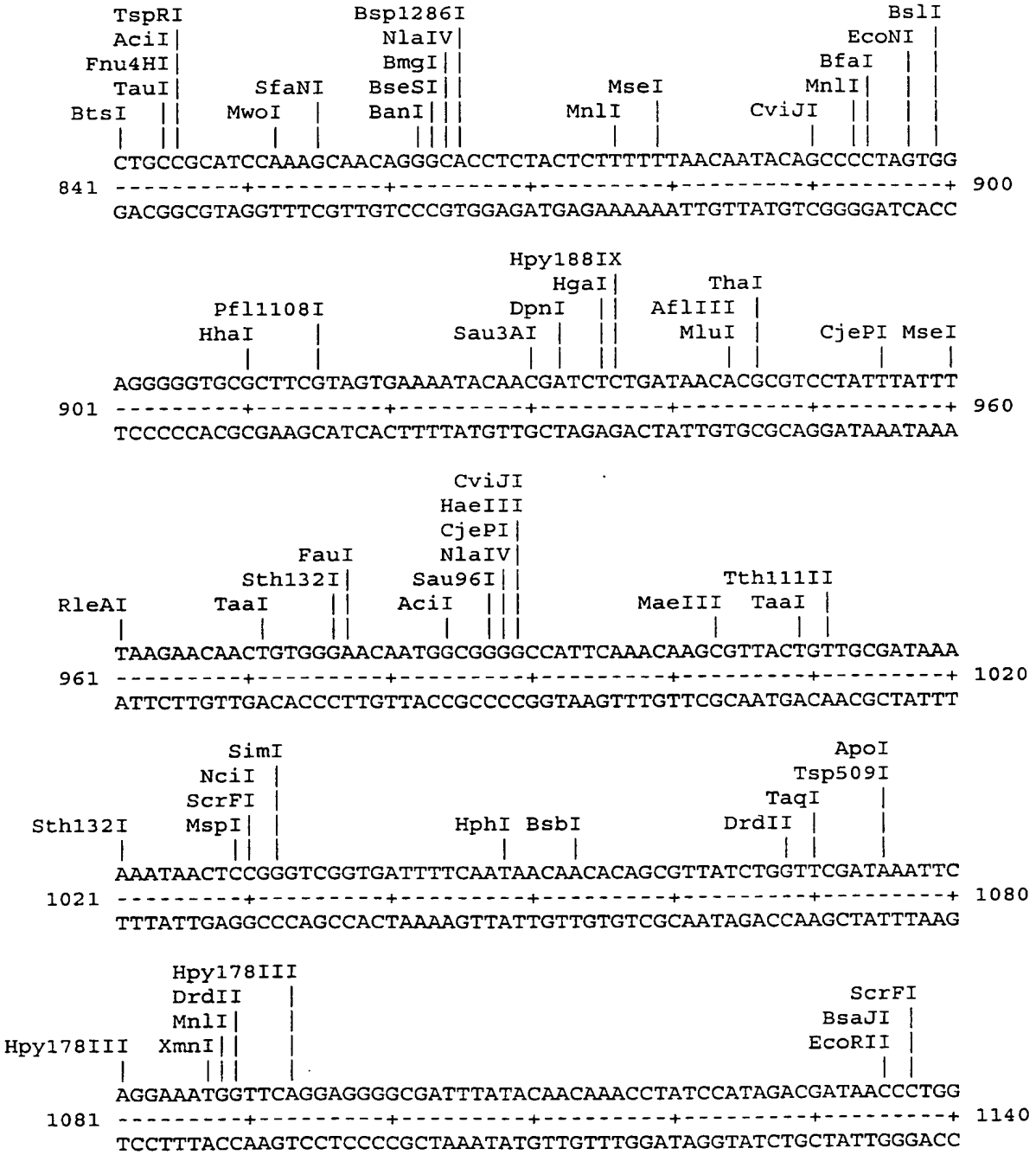
Fig. 22 (con't)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CviJI
BslI
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DpnI
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CjePI
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Sth132I
Sau96I
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TaaI
AciI
Tth111II
MaeIII
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NciI
ScrFI
Sth132I
MspI
HphI
BsbI
ApoI
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TaqI
DrdII
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EcoRII
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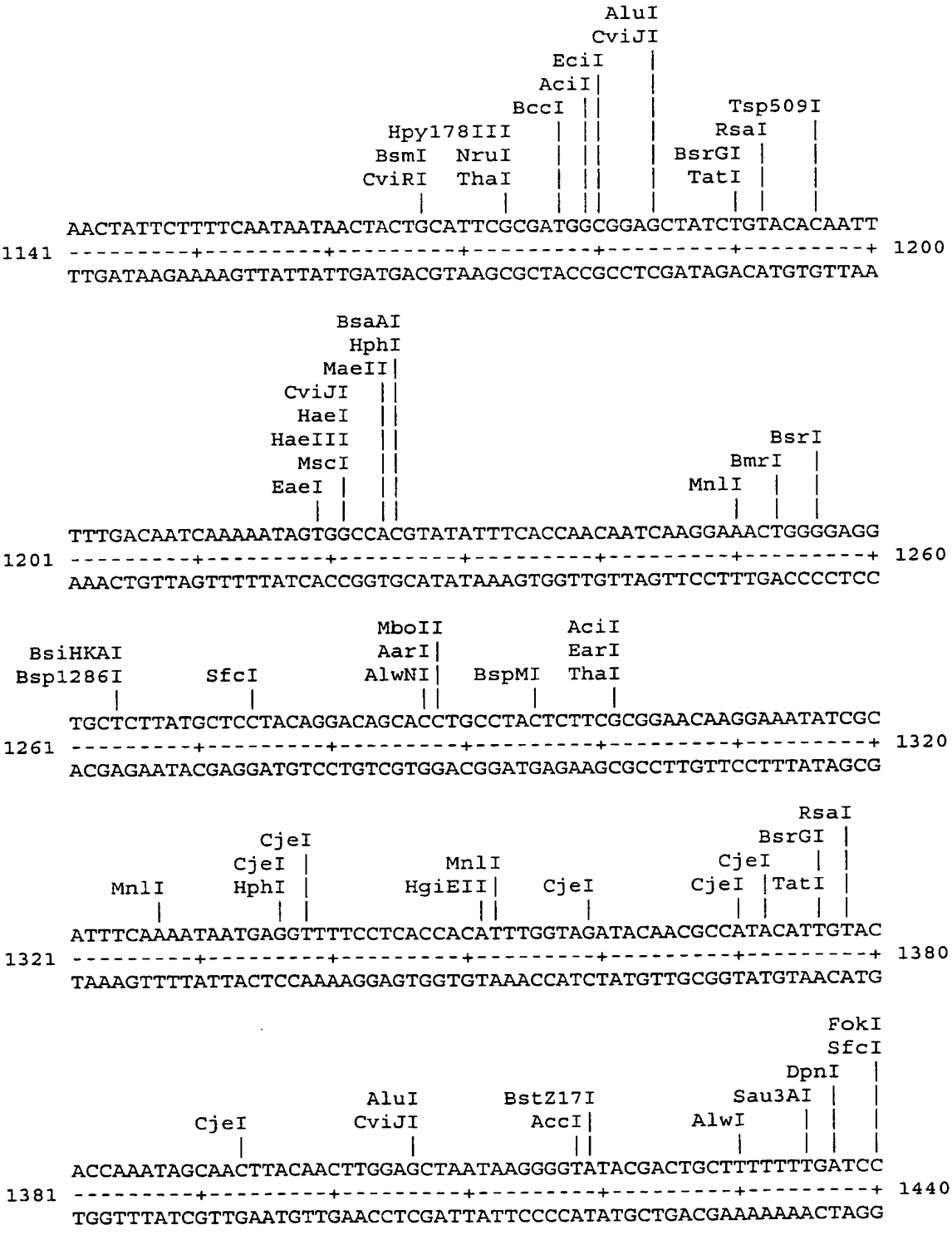
Fig. 22 (con't)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ThaI
TatI
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BmrI
EaeI
MnlI
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Bsp1286I
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AlwNI
BspMI
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CjeI
MnlI
CjeI
MnlI
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CjeI
CjeI
TatI
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1321 ---------+---------+---------+---------+---------+---------+ 1380
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FokI
SfcI
DpnI
AluI
BstZ17I
Sau3AI
CjeI
CviJI
AccI
AlwI
ACCAAATAGCAACTTACAACTTGGAGCTAATAAGGGGTATACGACTGCTTTTTTTGATCC
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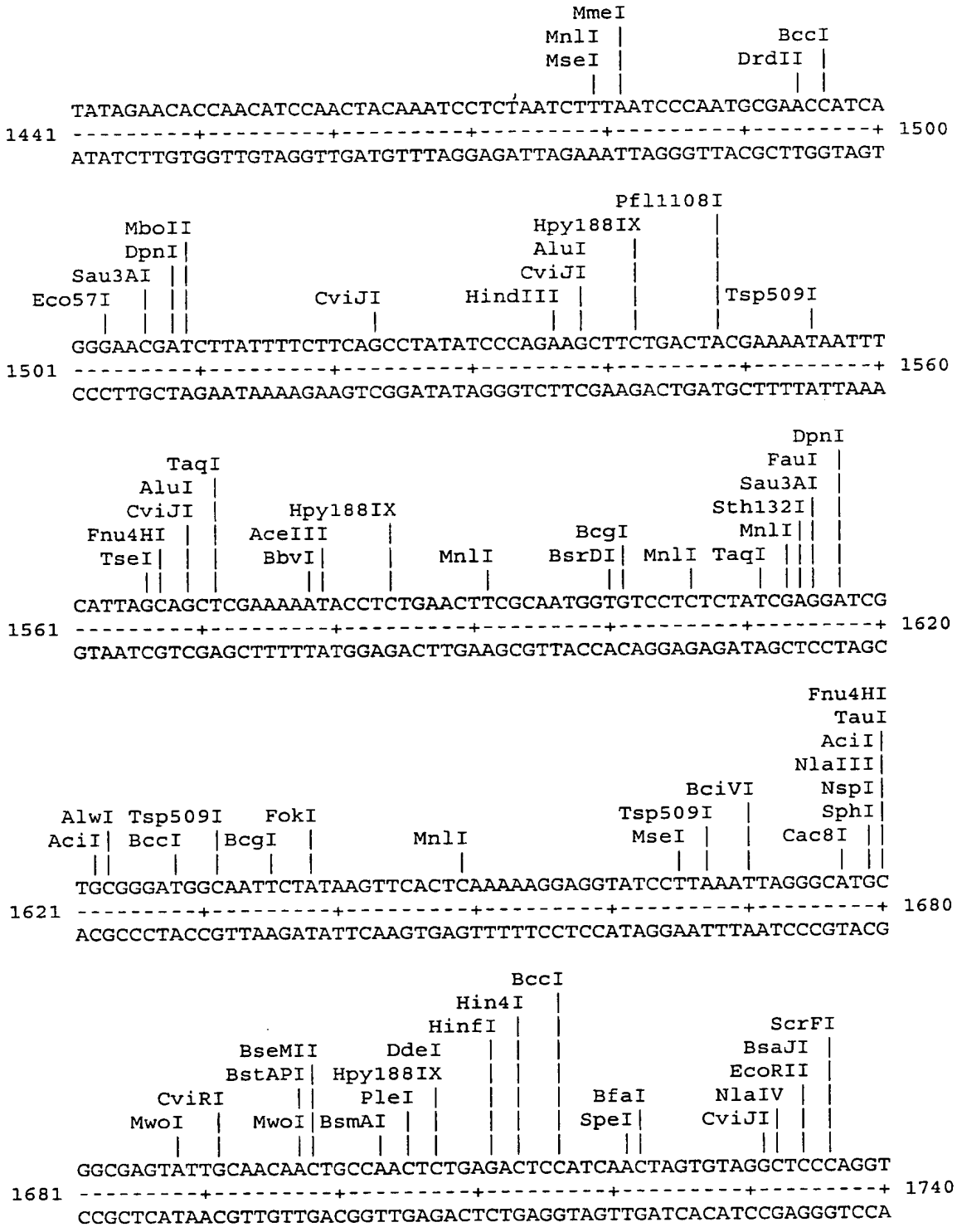
Fig. 22 (con't)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DpnI
Hpy188IX
AluI
Sau3AI
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Eco57I
CviJI
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TaqI
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BciVI
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BcgI
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SpeI
CviJI
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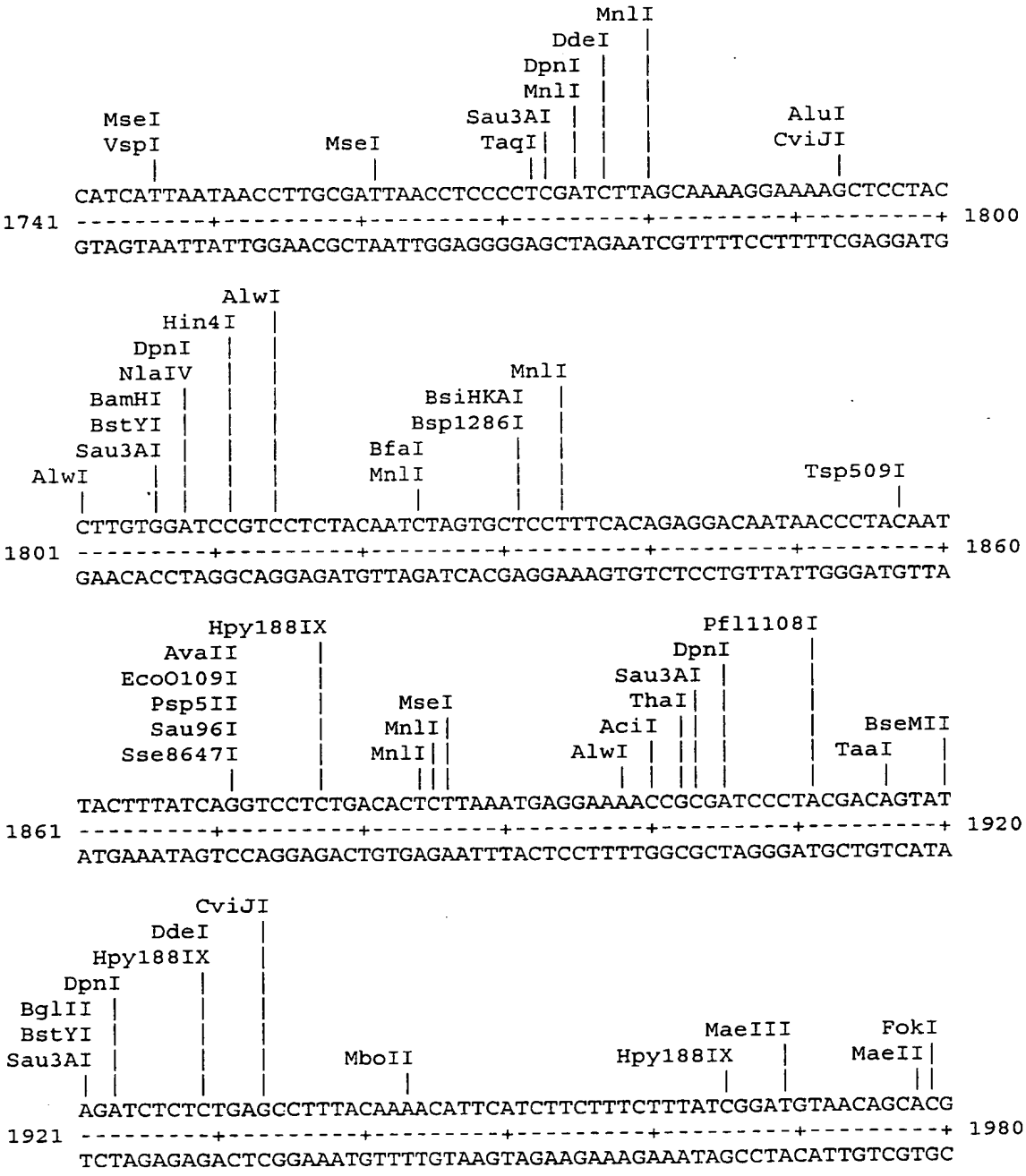
Fig. 22 (con't)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DpnI
NlaIV
BamHI
BstYI
Sau3AI
AlwI
MnlI
BsiHKAI
Bsp1286I
BfaI
MnlI
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DpnI
Sau3AI
ThaI
AciI
AlwI
BseMII
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DpnI
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MaeIII
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FokI
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Fig. 22 (con't)

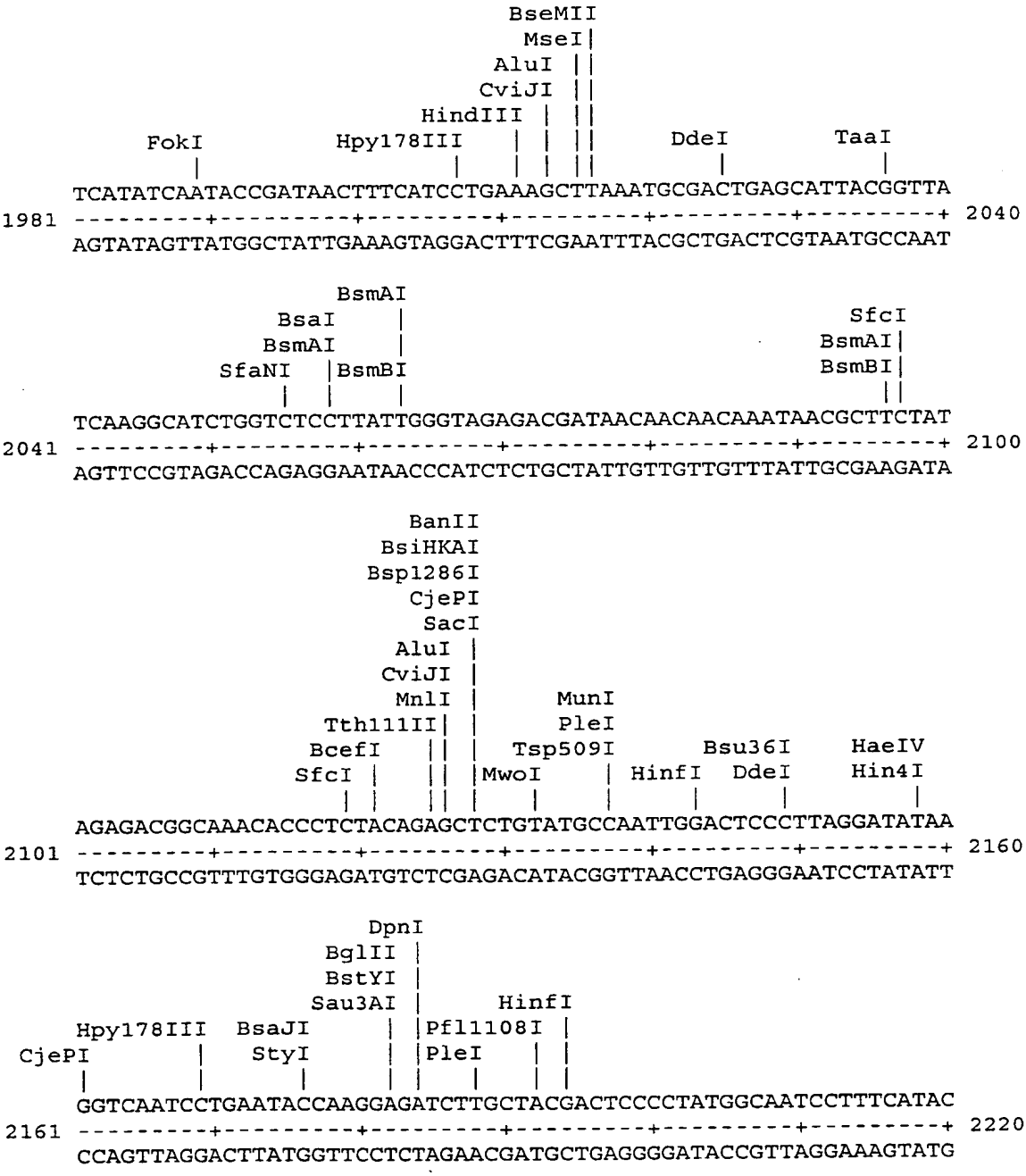
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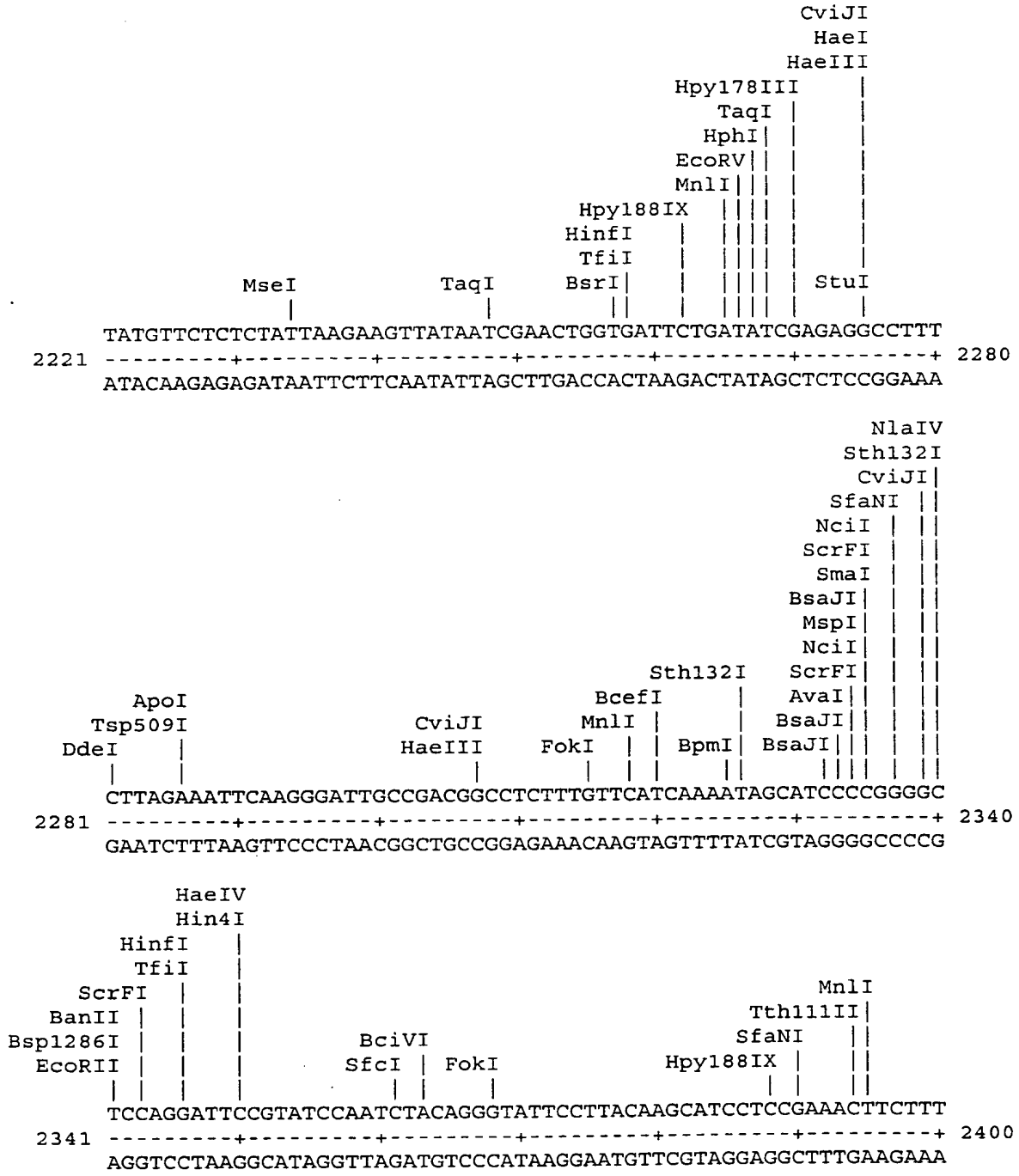
Fig. 22 (con't)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DdeI
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Hin4I
HinfI
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ScrFI
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Bsp1286I
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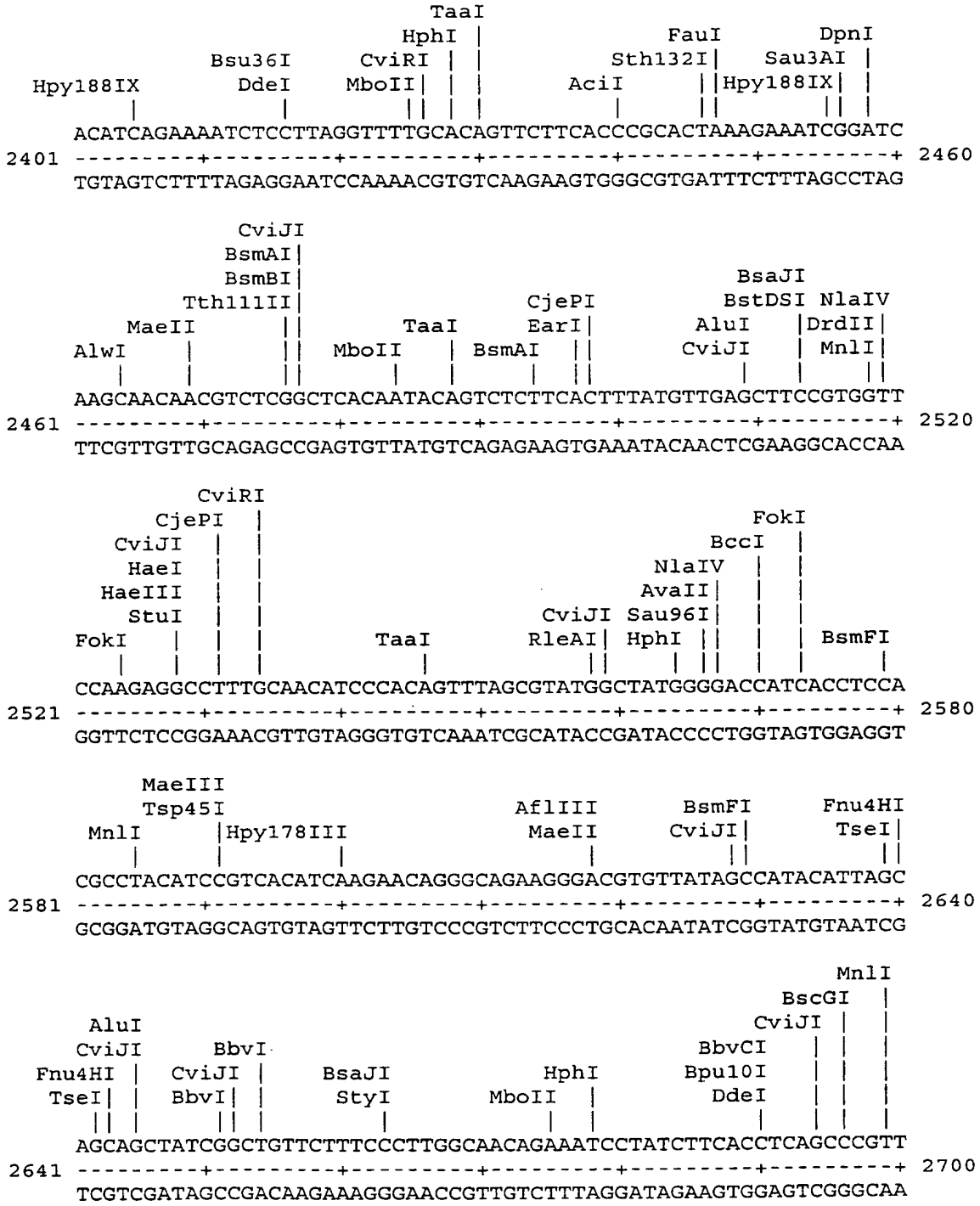
Fig. 22 (con't)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BsmBI
BsaJI
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CjePI
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EarI
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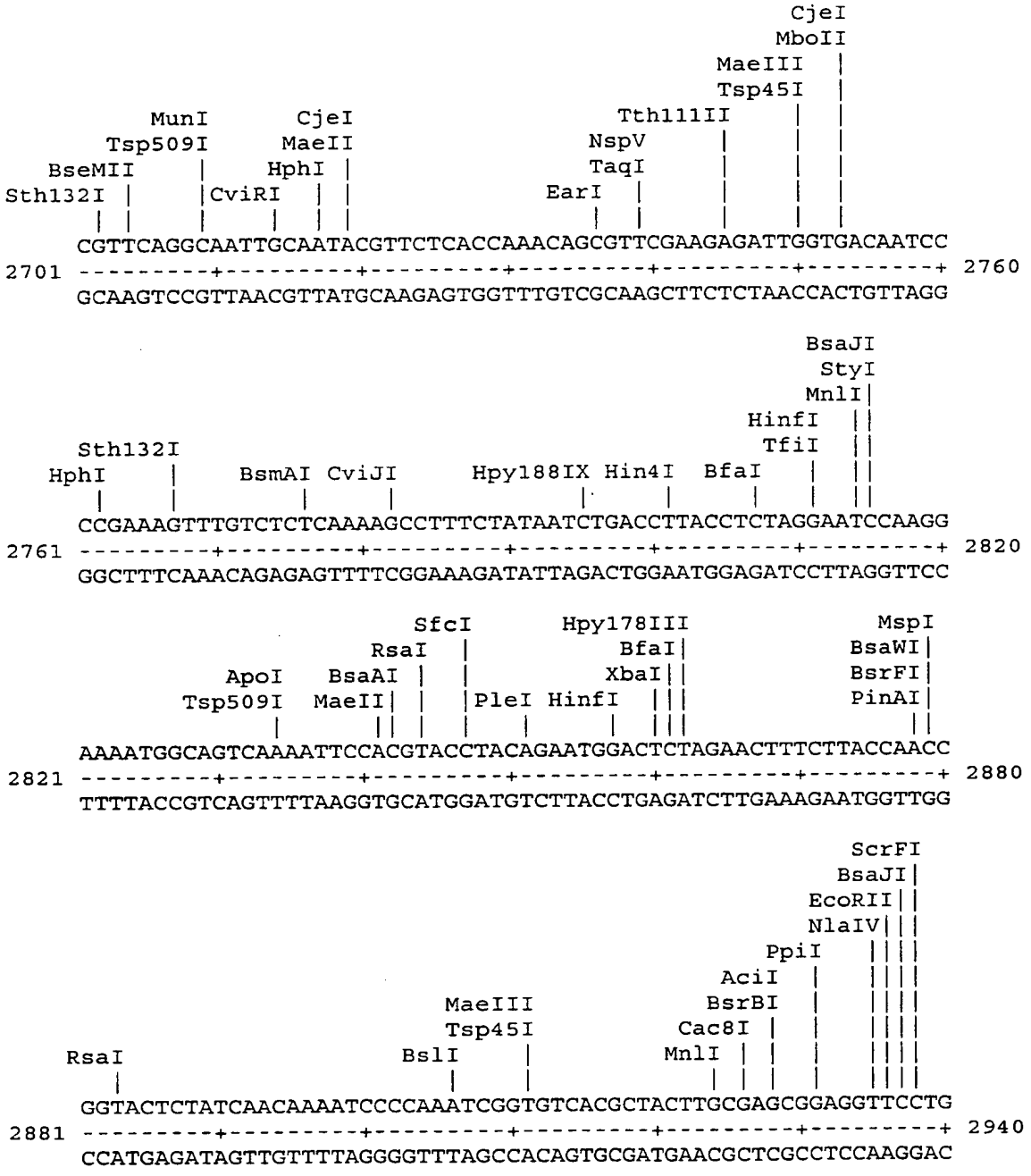
Fig. 22 (con't)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Tth111II
NspV
TaqI
EarI
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StyI
MnlI
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TfiI
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BfaI
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ApoI
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MaeII
PleI
HinfI
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NlaIV
PpiI
AciI
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MnlI
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RsaI
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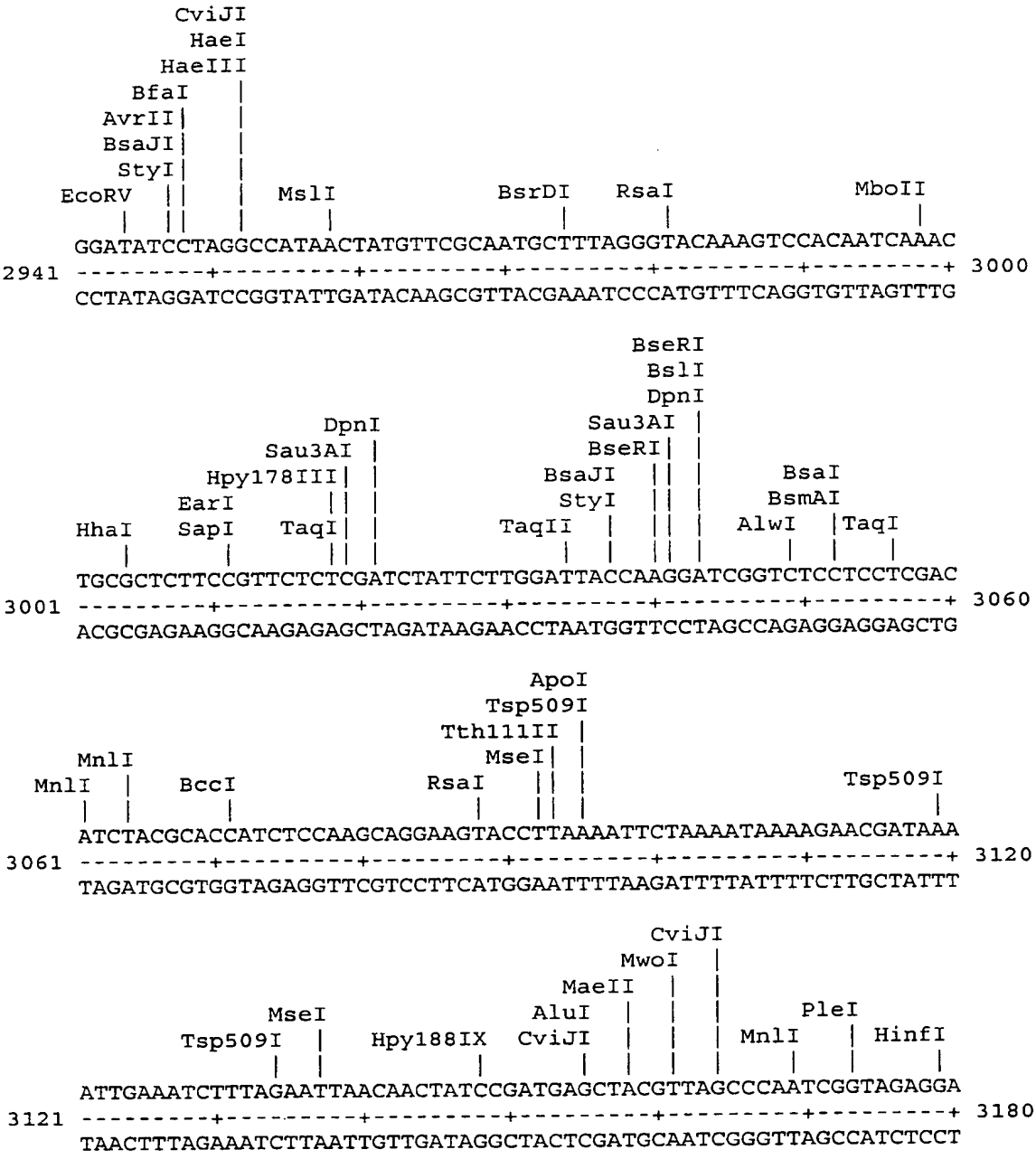
Fig. 22 (con't)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BslI
DpnI
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BseRI
BsaJI
StyI
BsaI
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TaqI
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CviJI
MwoI
MaeII
MseI
AluI
PleI
Tsp509I
Hpy188IX
CviJI
MnlI
HinfI
ATTGAAATCTTTAGAATTAACAACTATCCGATGAGCTACGTTAGCCCAATCGGTAGAGGA
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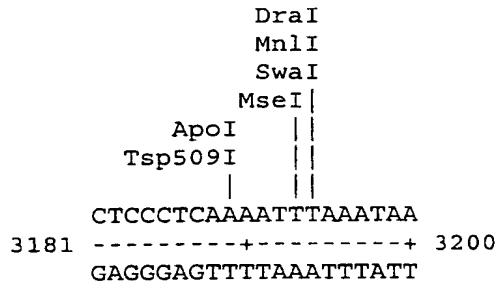
Fig. 22 (con't)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MnlI
SwaI
MseI
ApoI
Tsp509I
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3200
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Figure 23:

```
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tttctatttg tgaacgagta tgcgcttttt ttgcttcgga atg ttg ctt cct ttt   115
                                              Met Leu Leu Pro Phe
                                                1               5

act ttt gta ttg gct aat gaa ggt ctc caa ctt cct ttg gag acc tat   163
Thr Phe Val Leu Ala Asn Glu Gly Leu Gln Leu Pro Leu Glu Thr Tyr
                  10                  15                  20

att aca tta agt cct gaa tat caa gca gcc cct caa gta ggg ttt act   211
Ile Thr Leu Ser Pro Glu Tyr Gln Ala Ala Pro Gln Val Gly Phe Thr
              25                  30                  35

cat aac caa aat caa gat ctc gca att gtc ggg aat cac aat gat ttc   259
His Asn Gln Asn Gln Asp Leu Ala Ile Val Gly Asn His Asn Asp Phe
          40                  45                  50

atc ttg gac tat aag tac tat cgg tcg aat gga ggt gct ctt acc tgt   307
Ile Leu Asp Tyr Lys Tyr Tyr Arg Ser Asn Gly Gly Ala Leu Thr Cys
      55                  60                  65

aag aat ctt ctg atc tct gaa aat ata ggg aat gtc ttc ttt gag aag   355
Lys Asn Leu Leu Ile Ser Glu Asn Ile Gly Asn Val Phe Phe Glu Lys
  70                  75                  80                  85

aat gtc tgt ccc aat tct ggc ggg gca att tat gct gct caa aat tgc   403
Asn Val Cys Pro Asn Ser Gly Gly Ala Ile Tyr Ala Ala Gln Asn Cys
                  90                  95                 100

acg atc tcc aag aat cag aac tat gca ttt act aca aac ttg gtc tct   451
Thr Ile Ser Lys Asn Gln Asn Tyr Ala Phe Thr Thr Asn Leu Val Ser
             105                 110                 115

gac aat cct aca gcc act gcg gga tca cta ttg ggt gga gct ctc ttt   499
Asp Asn Pro Thr Ala Thr Ala Gly Ser Leu Leu Gly Gly Ala Leu Phe
         120                 125                 130

gcc ata aat tgc tct att act aat aac cta gga cag gga act ttc gtt   547
Ala Ile Asn Cys Ser Ile Thr Asn Asn Leu Gly Gln Gly Thr Phe Val
     135                 140                 145

gac aat ctc gct tta aat aag ggg ggt gcc ctc tat act gag acg aac   595
Asp Asn Leu Ala Leu Asn Lys Gly Gly Ala Leu Tyr Thr Glu Thr Asn
150                 155                 160                 165

tta tct att aaa gac aat aaa ggc ccg atc ata atc aag cag aat cgg   643
Leu Ser Ile Lys Asp Asn Lys Gly Pro Ile Ile Ile Lys Gln Asn Arg
                 170                 175                 180

gca cta aat tcg gac agt tta gga gga ggg att tat agt ggg aac tct   691
Ala Leu Asn Ser Asp Ser Leu Gly Gly Gly Ile Tyr Ser Gly Asn Ser
             185                 190                 195
```

Fig. 23 (con't)

```
cta aat ata gag gga aat tct gga gct ata cag atc aca agc aac tct   739
Leu Asn Ile Glu Gly Asn Ser Gly Ala Ile Gln Ile Thr Ser Asn Ser
        200                 205                 210

tca gga tct ggg gga ggc ata ttt tct acc caa aca ctc acg atc tcc   787
Ser Gly Ser Gly Gly Gly Ile Phe Ser Thr Gln Thr Leu Thr Ile Ser
    215                 220                 225

tcg aat aaa aaa ctc ata gaa atc agt gaa aat tcc gcg ttc gca aat   835
Ser Asn Lys Lys Leu Ile Glu Ile Ser Glu Asn Ser Ala Phe Ala Asn
230                 235                 240                 245

aac tat gga tcg aac ttc aat cca gga gga gga ggt ctt act acc acc   883
Asn Tyr Gly Ser Asn Phe Asn Pro Gly Gly Gly Gly Leu Thr Thr Thr
                250                 255                 260

ttt tgc acg ata ttg aac aac cga gaa ggg gta ctc ttt aac aat aac   931
Phe Cys Thr Ile Leu Asn Asn Arg Glu Gly Val Leu Phe Asn Asn Asn
            265                 270                 275

caa agc cag agc aac ggt gga gcc att cat gcg aaa tct atc att atc   979
Gln Ser Gln Ser Asn Gly Gly Ala Ile His Ala Lys Ser Ile Ile Ile
        280                 285                 290

aaa gaa aat ggt cct gta tac ttt tta aat aac act gca act cgg gga   1027
Lys Glu Asn Gly Pro Val Tyr Phe Leu Asn Asn Thr Ala Thr Arg Gly
    295                 300                 305

ggg gct ctc ctc aac tta tca gca ggt tct gga aac gga agc ttc atc   1075
Gly Ala Leu Leu Asn Leu Ser Ala Gly Ser Gly Asn Gly Ser Phe Ile
310                 315                 320                 325

tta tct gca gat aat gga gat att atc ttt aac aat aat acg gcc tcc   1123
Leu Ser Ala Asp Asn Gly Asp Ile Ile Phe Asn Asn Asn Thr Ala Ser
                330                 335                 340

aag cat gcc ctc aat cct cca tac aga aac gcc att cac tcg act cct   1171
Lys His Ala Leu Asn Pro Pro Tyr Arg Asn Ala Ile His Ser Thr Pro
            345                 350                 355

aat atg aat ctg caa ata gga gcc cgt ccc ggc tat cga gtg ctg ttc   1219
Asn Met Asn Leu Gln Ile Gly Ala Arg Pro Gly Tyr Arg Val Leu Phe
        360                 365                 370

tat gat ccc ata gaa cat gag ctc cct tcc tcc ttc ccc ata ctc ttt   1267
Tyr Asp Pro Ile Glu His Glu Leu Pro Ser Ser Phe Pro Ile Leu Phe
    375                 380                 385

aat ttc gaa acc ggt cat aca ggt aca gtt tta ttt tca ggg gaa cat   1315
Asn Phe Glu Thr Gly His Thr Gly Thr Val Leu Phe Ser Gly Glu His
390                 395                 400                 405
```

Fig. 23 (con't)

```
gta cac cag aac ttt acc gat gaa atg aat ttc ttt tcc tat tta agg   1363
Val His Gln Asn Phe Thr Asp Glu Met Asn Phe Phe Ser Tyr Leu Arg
                410                 415                 420

aac act tcg gaa cta cgt caa gga gtc ctt gct gtt gaa gat ggt gcg   1411
Asn Thr Ser Glu Leu Arg Gln Gly Val Leu Ala Val Glu Asp Gly Ala
            425                 430                 435

ggg ctg gcc tgc tat aag ttc ttc caa cga gga ggc act cta ctt cta   1459
Gly Leu Ala Cys Tyr Lys Phe Phe Gln Arg Gly Gly Thr Leu Leu Leu
        440                 445                 450

ggt caa ggt gcg gtg atc acg aca gca gga acg att ccc aca cca tcc   1507
Gly Gln Gly Ala Val Ile Thr Thr Ala Gly Thr Ile Pro Thr Pro Ser
    455                 460                 465

tca aca cca acg aca gta gga agt act ata act tta aat cac att gcc   1555
Ser Thr Pro Thr Thr Val Gly Ser Thr Ile Thr Leu Asn His Ile Ala
470                 475                 480                 485

att gac ctt cct tct att ctt tct ttt caa gct cag gct cca aaa att   1603
Ile Asp Leu Pro Ser Ile Leu Ser Phe Gln Ala Gln Ala Pro Lys Ile
                490                 495                 500

tgg att tac ccc aca aaa aca gga tct acc tat act gaa gat tcc aac   1651
Trp Ile Tyr Pro Thr Lys Thr Gly Ser Thr Tyr Thr Glu Asp Ser Asn
            505                 510                 515

ccg aca atc aca atc tca gga act ctc acc tta cgc aac agc aac aac   1699
Pro Thr Ile Thr Ile Ser Gly Thr Leu Thr Leu Arg Asn Ser Asn Asn
        520                 525                 530

gaa gat ccc tac gat agt ctg gat ctc tcg cac tct ctt gag aaa gtt   1747
Glu Asp Pro Tyr Asp Ser Leu Asp Leu Ser His Ser Leu Glu Lys Val
    535                 540                 545

ccc ctt ctt tat att gtc gat gtc gct gca caa aaa att aac tct tcg   1795
Pro Leu Leu Tyr Ile Val Asp Val Ala Ala Gln Lys Ile Asn Ser Ser
550                 555                 560                 565

caa ctg gat cta tcc aca tta aat tct ggc gaa cac tat ggg tat caa   1843
Gln Leu Asp Leu Ser Thr Leu Asn Ser Gly Glu His Tyr Gly Tyr Gln
                570                 575                 580

ggc atc tgg tcg acc tat tgg gta gaa act aca aca atc acg aac cct   1891
Gly Ile Trp Ser Thr Tyr Trp Val Glu Thr Thr Thr Ile Thr Asn Pro
            585                 590                 595

aca tct cta cta ggc gcg aat aca aaa cac aag ctg ctc tat gca aac   1939
Thr Ser Leu Leu Gly Ala Asn Thr Lys His Lys Leu Leu Tyr Ala Asn
        600                 605                 610
```

Fig. 23 (con't)

```
tgg tct cct cta ggc tac cgt cct cat ccc gaa cgt cga gga gaa ttc   1987
Trp Ser Pro Leu Gly Tyr Arg Pro His Pro Glu Arg Arg Gly Glu Phe
    615                 620                 625

att acg aat gcc ttg tgg caa tcg gca tat acg gct ctt gca gga ctc   2035
Ile Thr Asn Ala Leu Trp Gln Ser Ala Tyr Thr Ala Leu Ala Gly Leu
630                 635                 640                 645

cac tcc ctc tcc tcc tgg gat gaa gag aag ggt cat gca gct tcc cta   2083
His Ser Leu Ser Ser Trp Asp Glu Glu Lys Gly His Ala Ala Ser Leu
                650                 655                 660

caa ggc att ggt ctt ctg gtt cat caa aaa gac aaa aac ggt ttt aag   2131
Gln Gly Ile Gly Leu Leu Val His Gln Lys Asp Lys Asn Gly Phe Lys
            665                 670                 675

gga ttt cgt agt cat atg aca ggt tat agt gct acc acc gaa gca acc   2179
Gly Phe Arg Ser His Met Thr Gly Tyr Ser Ala Thr Thr Glu Ala Thr
        680                 685                 690

tct tct caa agt ccg aat ttc tct tta gga ttt gct cag ttc ttc tcc   2227
Ser Ser Gln Ser Pro Asn Phe Ser Leu Gly Phe Ala Gln Phe Phe Ser
    695                 700                 705

aaa gct aaa gaa cat gaa tct caa aat agc acg tcc tct cac cac tat   2275
Lys Ala Lys Glu His Glu Ser Gln Asn Ser Thr Ser Ser His His Tyr
710                 715                 720                 725

ttc tct gga atg tgc ata gca aaa tac tct ctt caa aga gtg ata cgt   2323
Phe Ser Gly Met Cys Ile Ala Lys Tyr Ser Leu Gln Arg Val Ile Arg
                730                 735                 740

cta tct gtg tct ctt gct tat atg ttt acc tcg gaa cat acc cat aca   2371
Leu Ser Val Ser Leu Ala Tyr Met Phe Thr Ser Glu His Thr His Thr
            745                 750                 755

atg tat cag ggt ctc ctg gaa ggg aac tct cag gga tct ttc cac aac   2419
Met Tyr Gln Gly Leu Leu Glu Gly Asn Ser Gln Gly Ser Phe His Asn
        760                 765                 770

cat acc tta gca ggg gct ctc tcc tgt gtt ttc tta cct caa cct cac   2467
His Thr Leu Ala Gly Ala Leu Ser Cys Val Phe Leu Pro Gln Pro His
    775                 780                 785

ggc gag tcc ctg cag atc tat ccc ttt att act gcc tta gcc atc cga   2515
Gly Glu Ser Leu Gln Ile Tyr Pro Phe Ile Thr Ala Leu Ala Ile Arg
790                 795                 800                 805

gga aat ctt gct gcg ttt caa gaa tct gga gac cat gct cgg gaa ttt   2563
Gly Asn Leu Ala Ala Phe Gln Glu Ser Gly Asp His Ala Arg Glu Phe
                810                 815                 820
```

Fig. 23 (con't)

```
tcc cta cac cgc ccc cta acg gac gtc tcc ctc cct gta gga atc cgc   2611
Ser Leu His Arg Pro Leu Thr Asp Val Ser Leu Pro Val Gly Ile Arg
            825                 830                 835

gct tct tgg aag aac cac cac cga gtt ccc cta gtc tgg ctc aca gaa   2659
Ala Ser Trp Lys Asn His His Arg Val Pro Leu Val Trp Leu Thr Glu
        840                 845                 850

att tcc tat cgc tct act ctc tat agg caa gat cct gaa ctc cac tcg   2707
Ile Ser Tyr Arg Ser Thr Leu Tyr Arg Gln Asp Pro Glu Leu His Ser
    855                 860                 865

aaa tta ctg att agc caa ggt acg tgg acg acg cag gcc act cct gtg   2755
Lys Leu Leu Ile Ser Gln Gly Thr Trp Thr Thr Gln Ala Thr Pro Val
870                 875                 880                 885

acc tac aat gct tta ggg atc aaa gtg aaa aat acc atg cag gtg ttt   2803
Thr Tyr Asn Ala Leu Gly Ile Lys Val Lys Asn Thr Met Gln Val Phe
                890                 895                 900

cct aaa gtc act ctc tcc tta gat tac tct gcg gat att tct tcc tcc   2851
Pro Lys Val Thr Leu Ser Leu Asp Tyr Ser Ala Asp Ile Ser Ser Ser
            905                 910                 915

acg ctg agt cac tac tta aac gtg gcg agt aga atg aga ttt           2893
Thr Leu Ser His Tyr Leu Asn Val Ala Ser Arg Met Arg Phe
        920                 925                 930

taacaataag tgaccaaaac agaaagatta aggaacctct agtgtcaaag actcctccta 2953

agtttttatt ctatctcggg aatttcacag cctgcatgtt cgggatg               3000
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Figure 24 (RY-46)

Restriction enzyme analysis of CPN100628

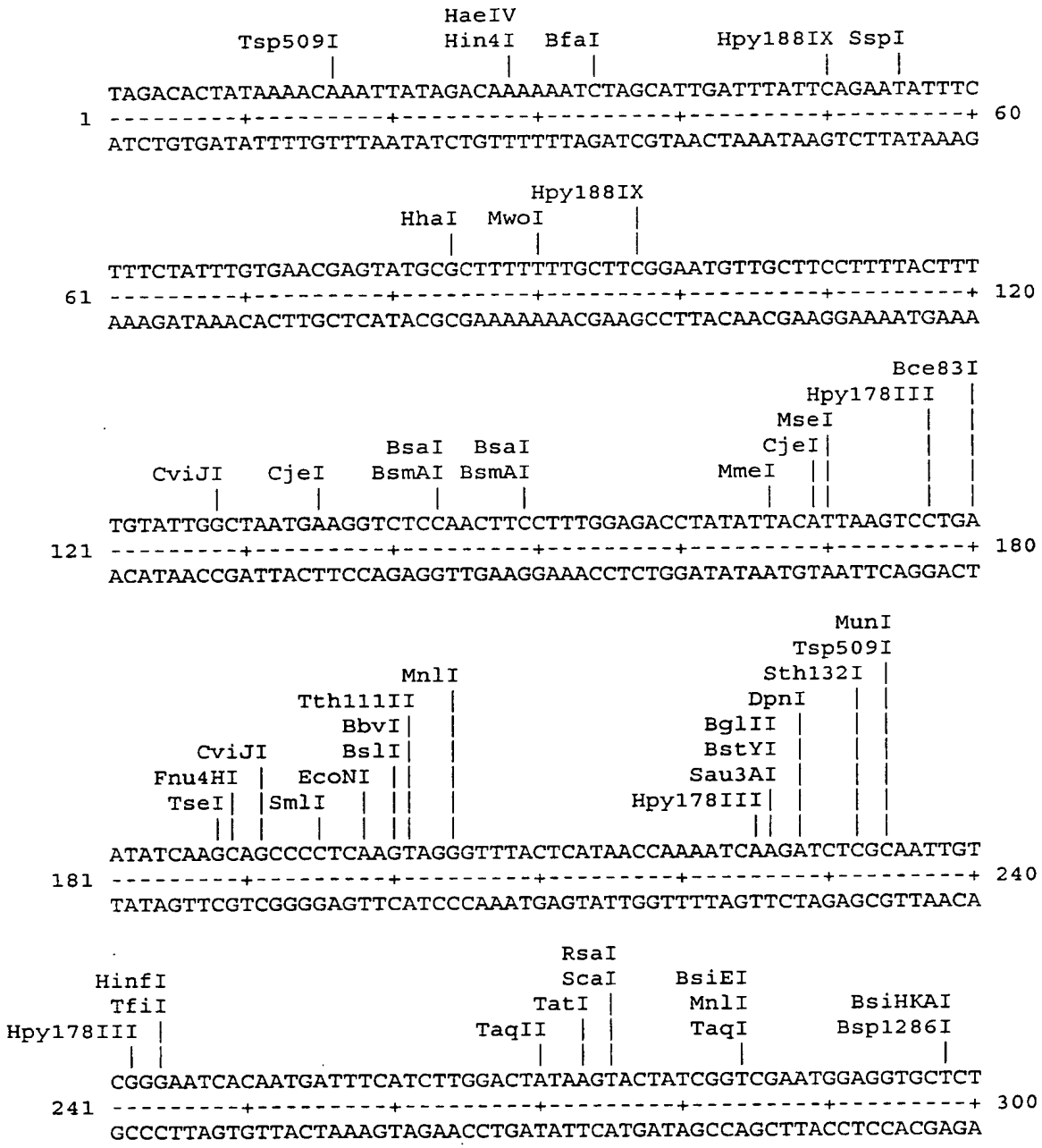
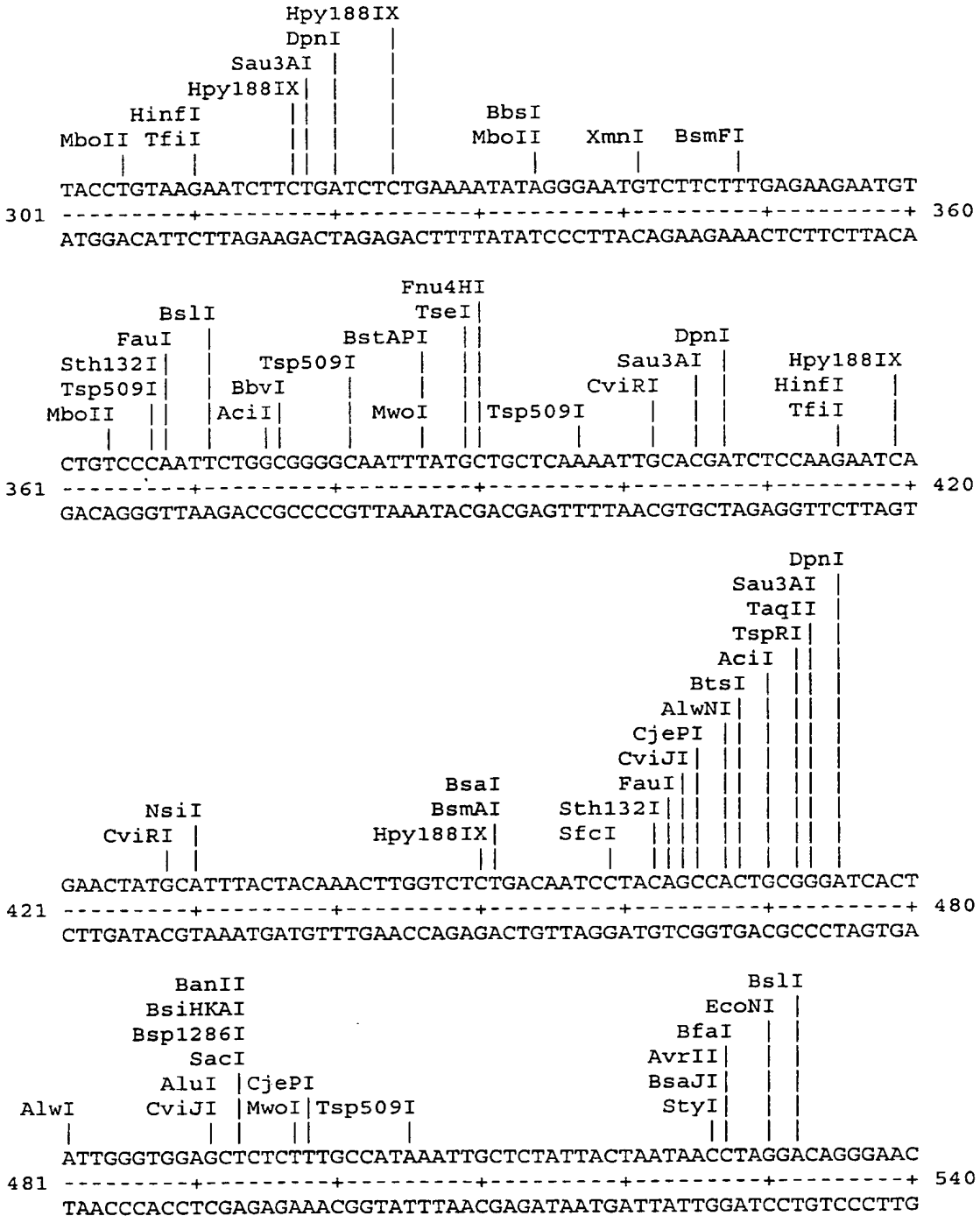


Fig. 24 (con't)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361
420
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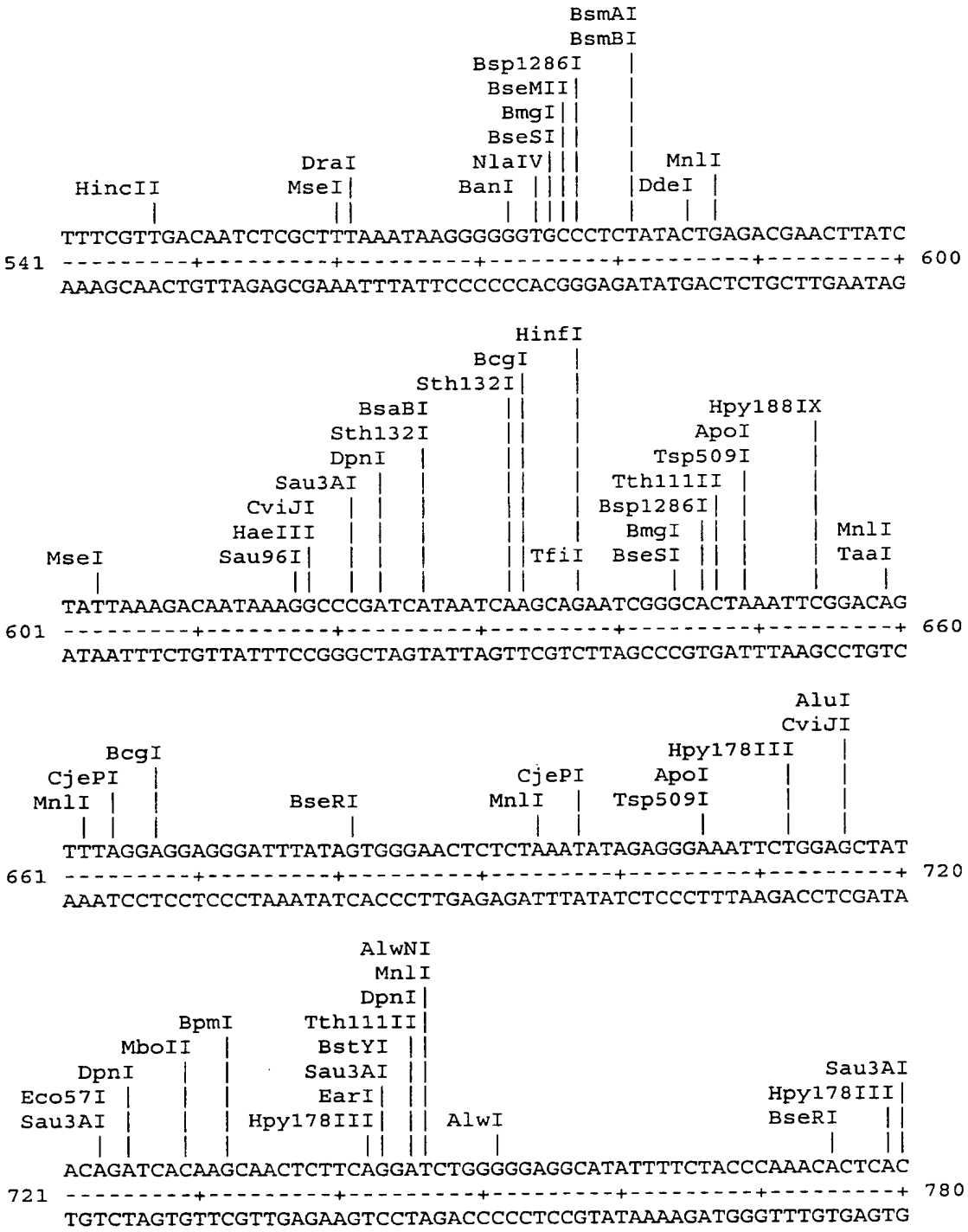
Fig. 24 (con't)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DdeI
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BcgI
Sth132I
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Sth132I
DpnI
Hpy188IX
ApoI
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Sau3AI
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HaeIII
BmgI
MnlI
MseI
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TfiI
BseSI
TaaI
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AluI
CviJI
BcgI
Hpy178III
CjePI
CjePI
ApoI
MnlI
BseRI
MnlI
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DpnI
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Hpy178III
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BseRI
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Fig. 24 (con't)

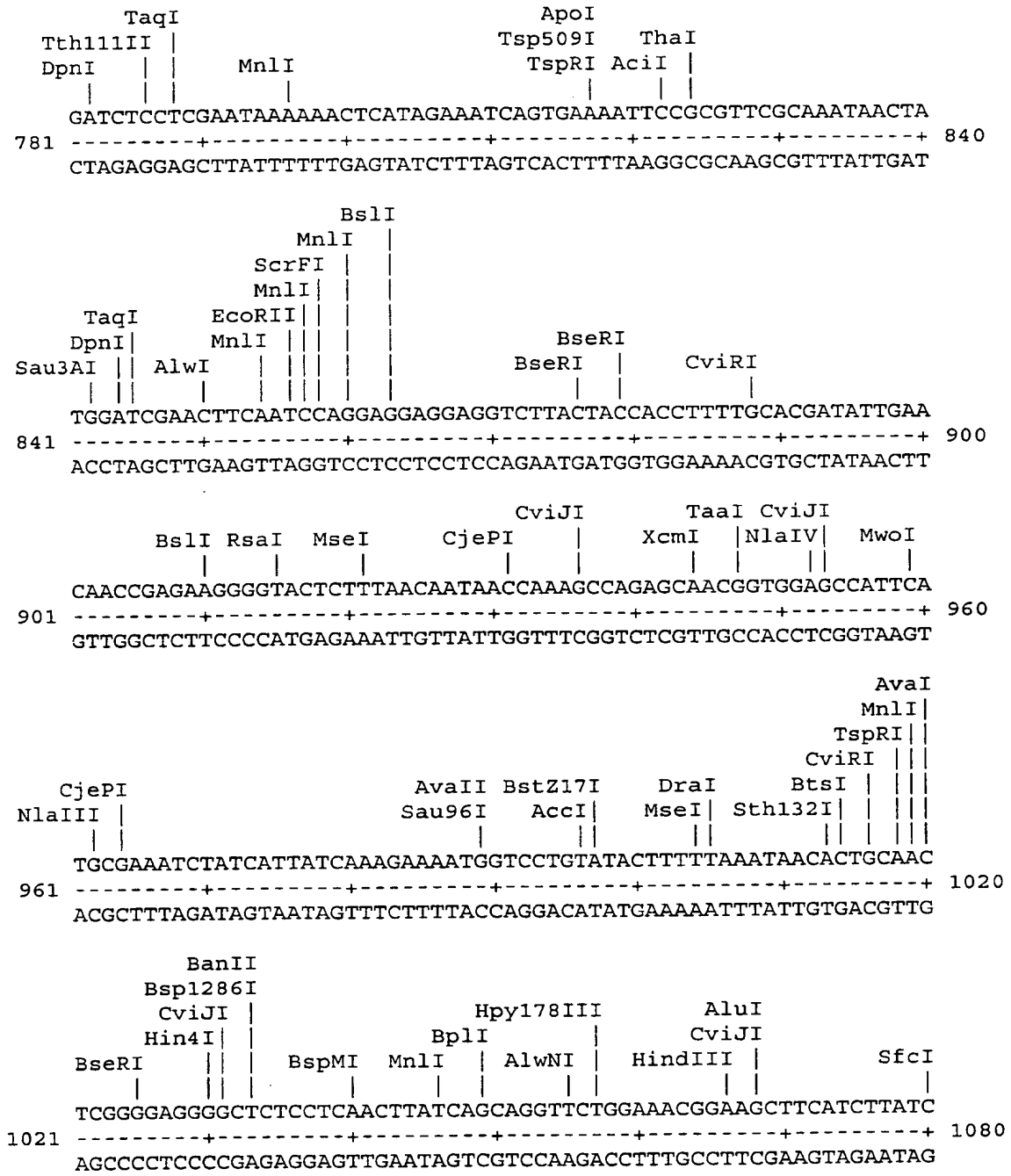
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Fig. 24 (con't)

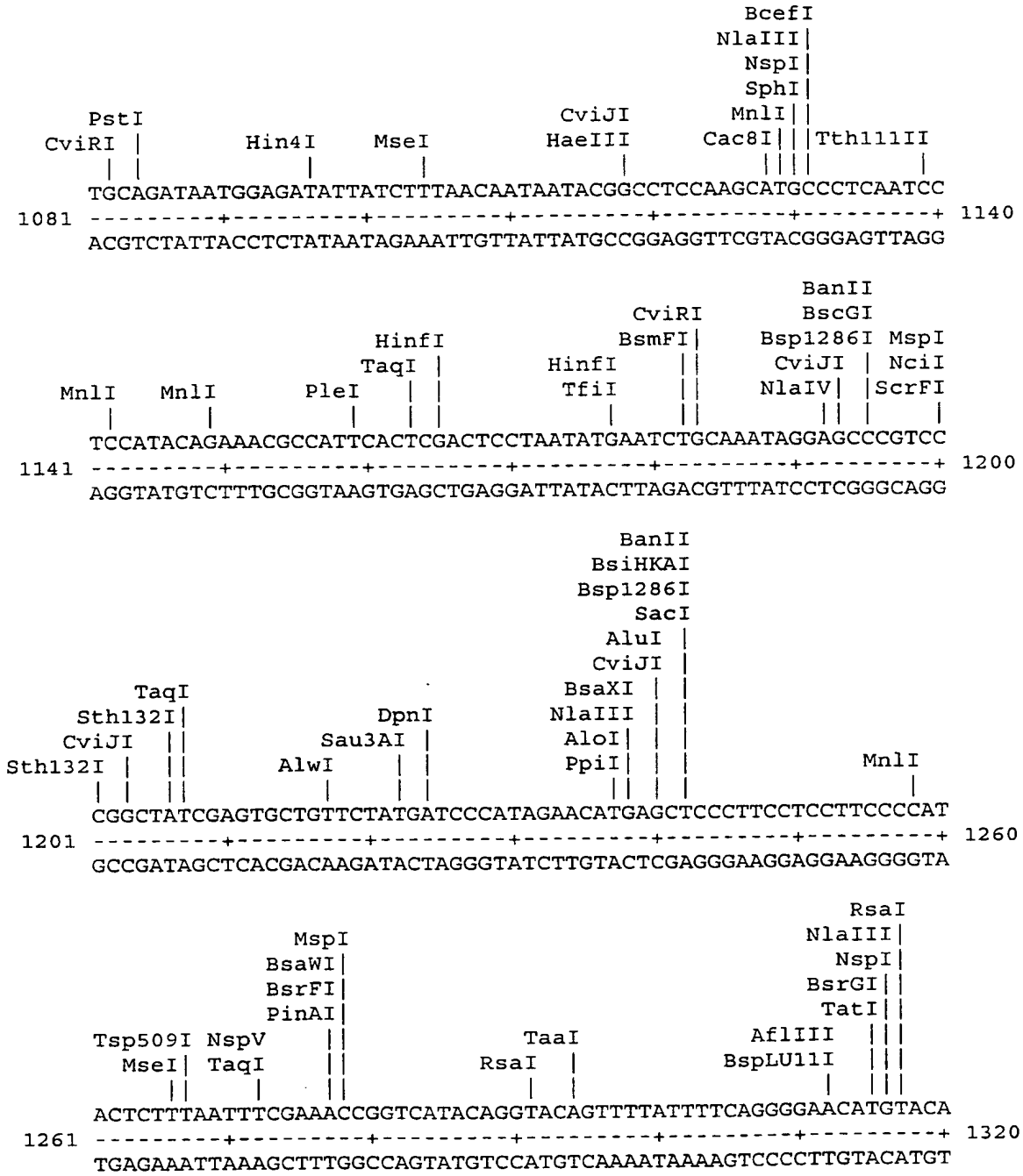
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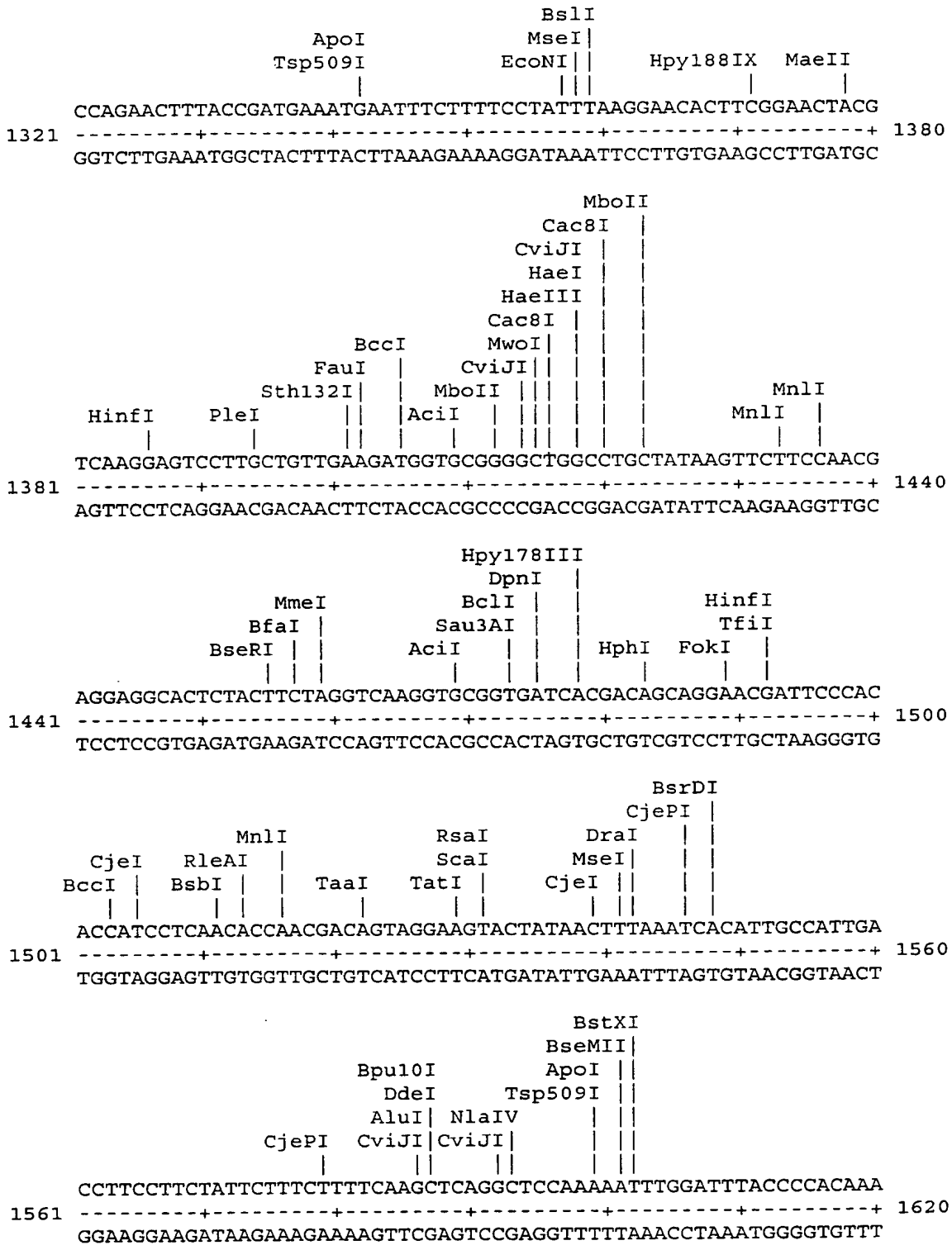
Fig. 24 (con't)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CjeI
RleAI
ScaI
MseI
BccI
BsbI
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TatI
CjeI
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BseMII
Bpu10I
ApoI
DdeI
Tsp509I
AluI
NlaIV
CjePI
CviJI
CviJI
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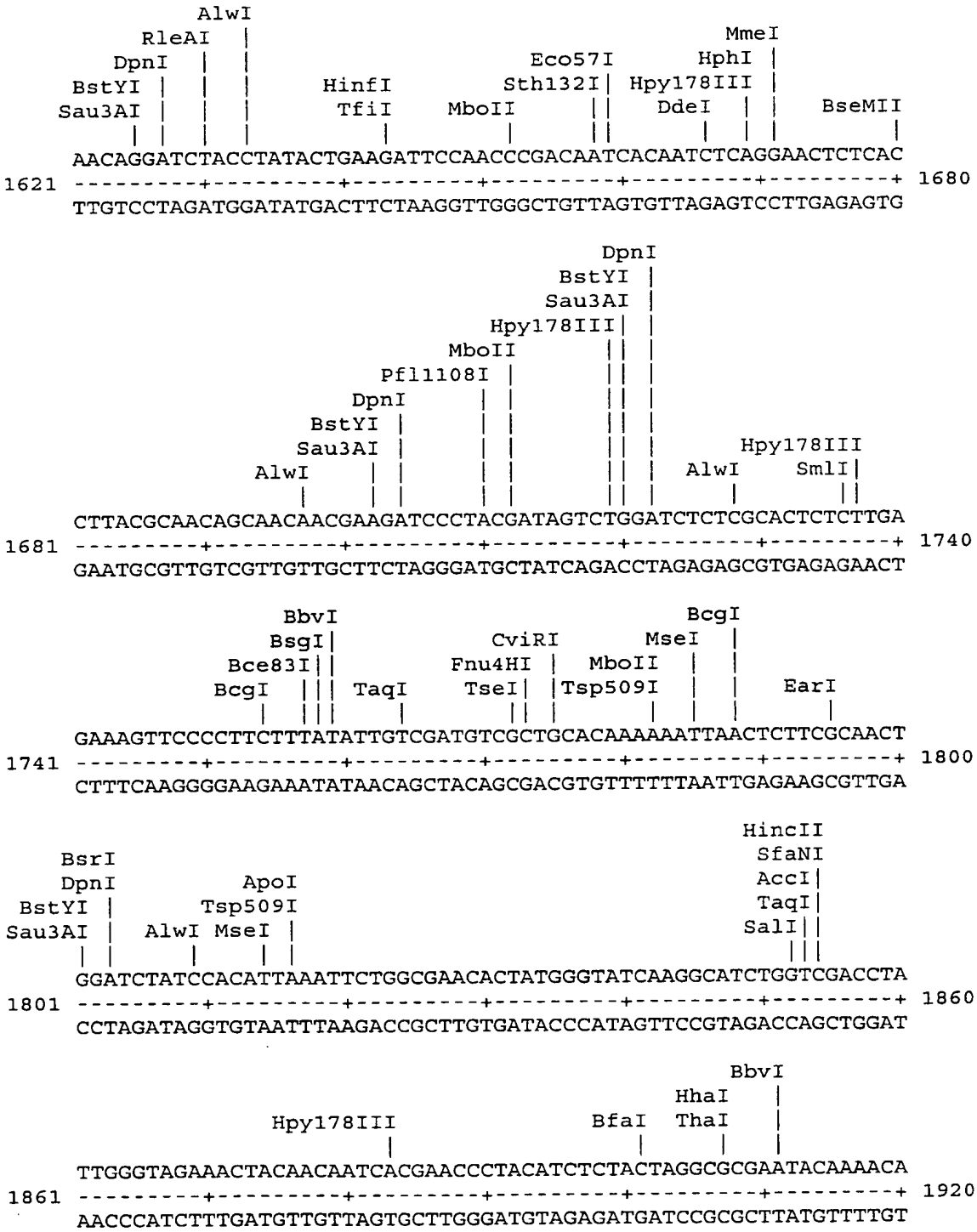
Fig. 24 (con't)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TaqI
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DpnI
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HhaI
ThaI
Hpy178III
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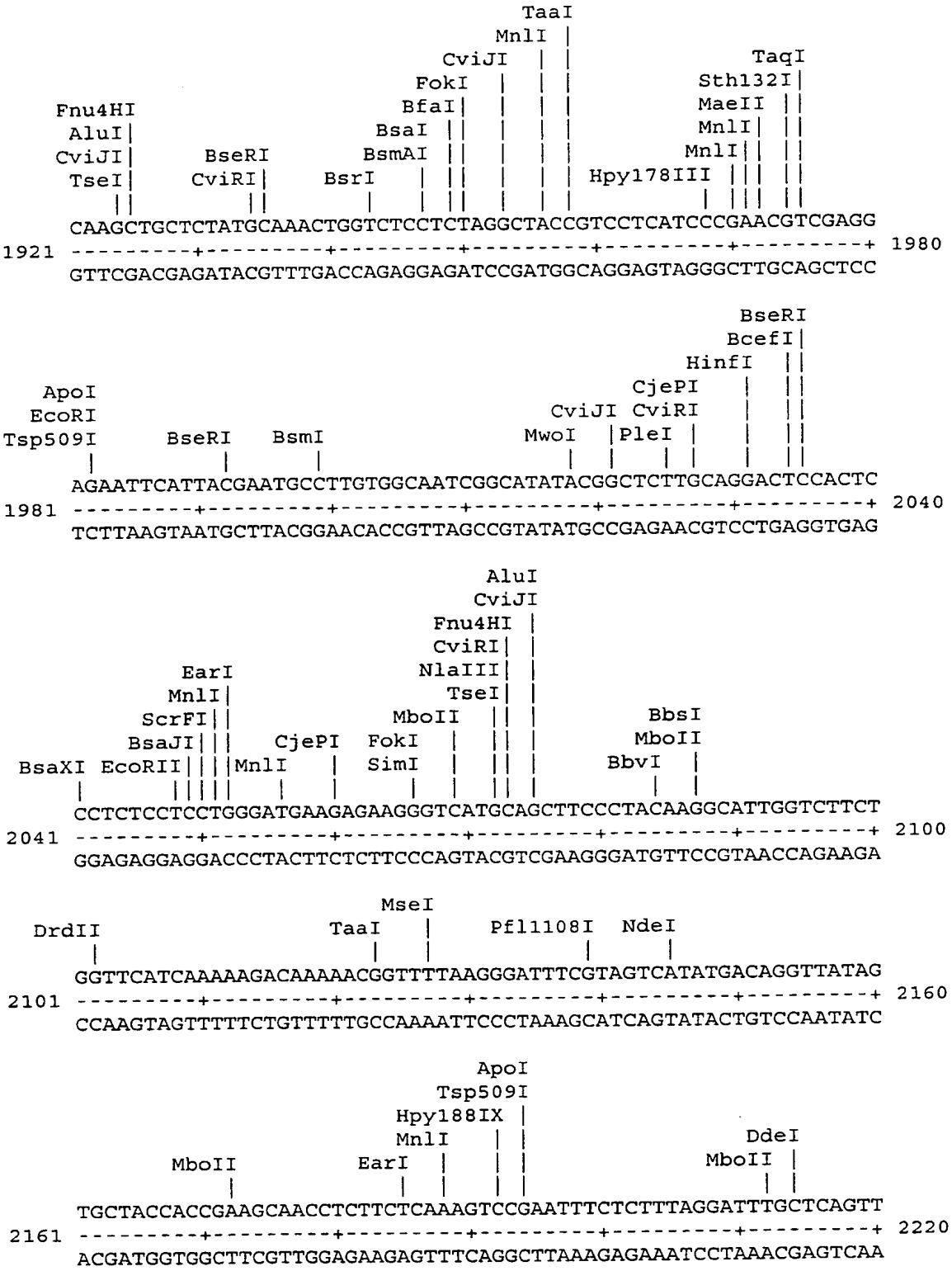
Fig. 24 (con't)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Hpy178III
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BcefI
HinfI
ApoI
CjePI
EcoRI
CviJI CviRI
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BsmI
MwoI
PleI
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CviRI
EarI
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MnlI
TseI
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BbsI
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FokI
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BsaXI
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MnlI
SimI
BbvI
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TaaI
Pfl1108I
NdeI
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Tsp509I
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DdeI
MboII
EarI
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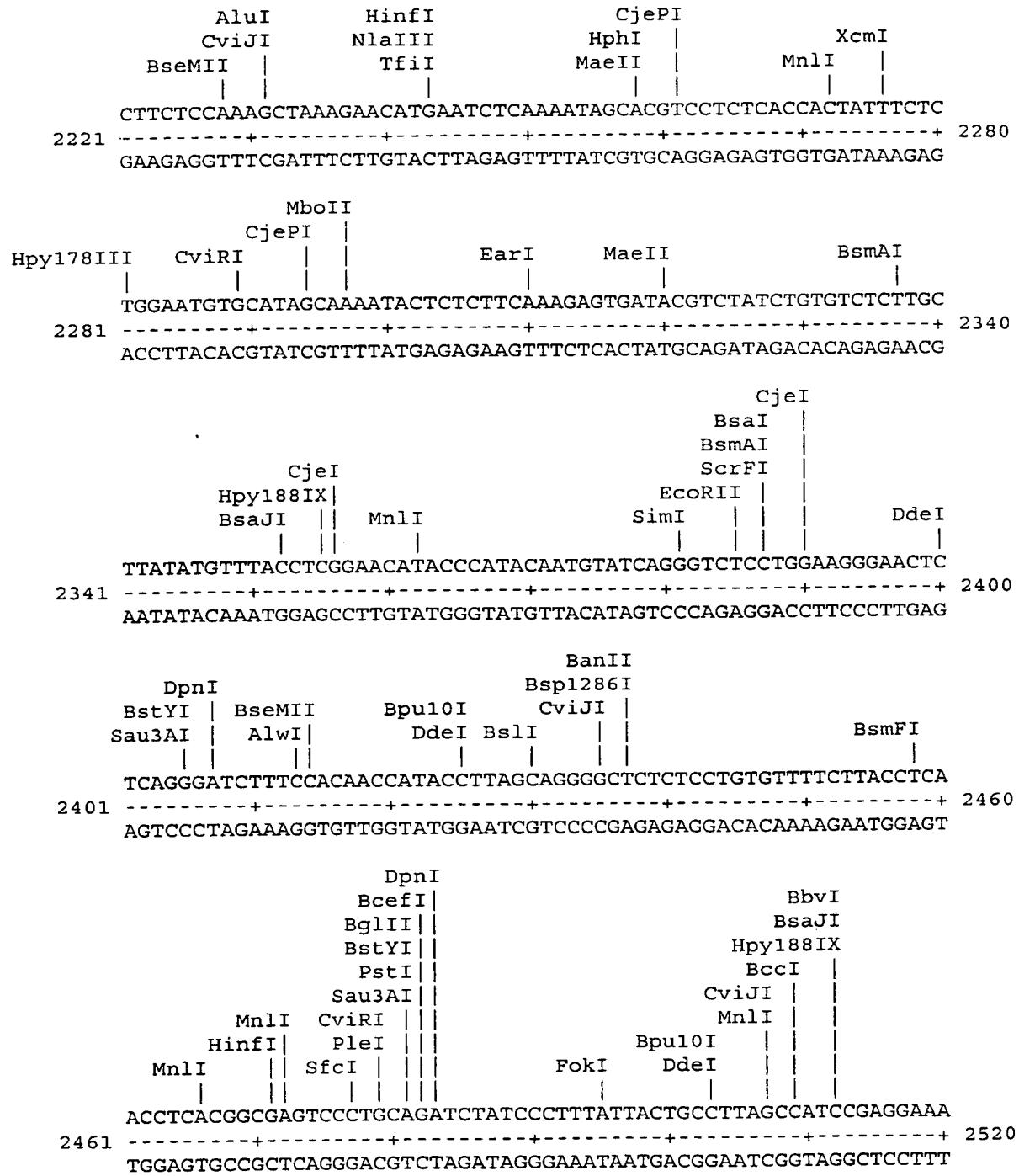
Fig. 24 (con't)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DpnI
BstYI
BseMII
Sau3AI
AlwI
Bpu10I
DdeI
BslI
CviJI
BsmFI
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BcefI
BglII
BstYI
PstI
Sau3AI
MnlI
CviRI
HinfI
PleI
MnlI
SfcI
BbvI
BsaJI
Hpy188IX
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CviJI
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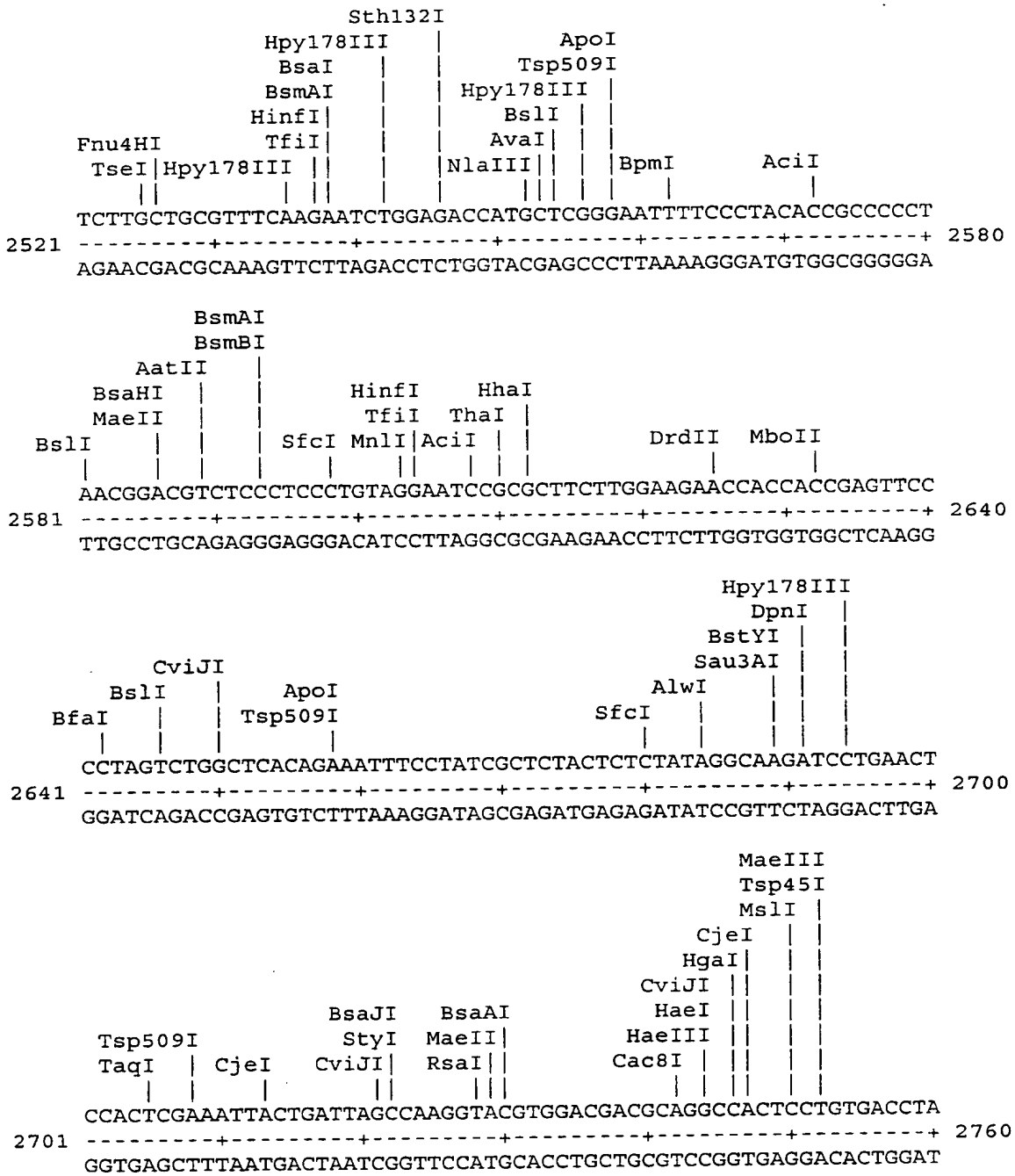
Fig. 24 (con't)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NlaIII
BpmI
AciI
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DpnI
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Sau3AI
CviJI
AlwI
BslI
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BfaI
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Tsp45I
MslI
CjeI
HgaI
CviJI
HaeI
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HaeIII
Tsp509I
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RsaI
Cac8I
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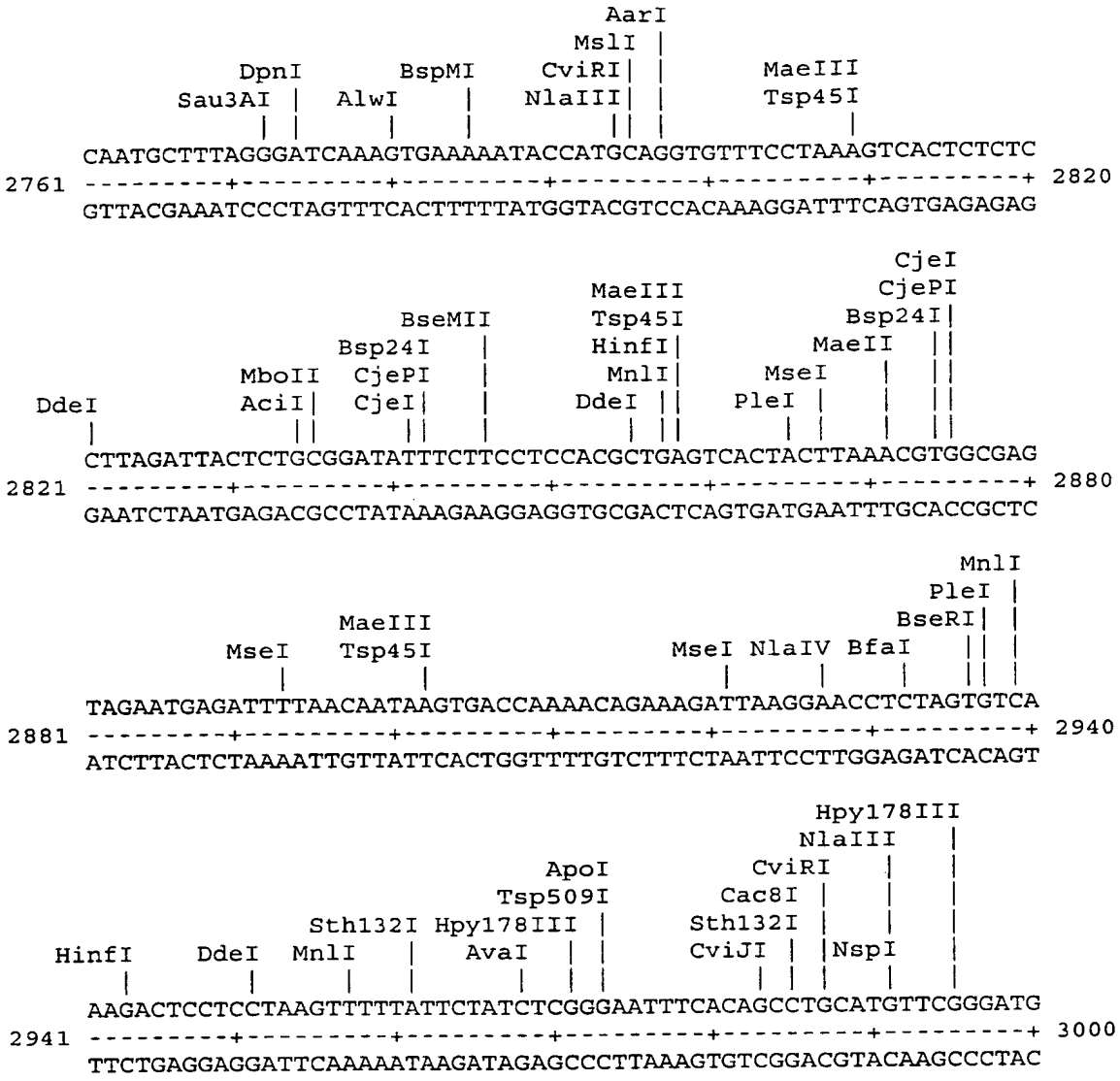
Fig. 24 (con't)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MaeII
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CviRI
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Figure 25:

```
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attacgattt taaaccttat ttaacgacag ggttgaggc atg cct ctt tct ttc    114
                                          Met Pro Leu Ser Phe
                                            1               5

aaa tct tca tct ttt tgt cta ctt gcc tgt tta tgt agt gca agt tgc   162
Lys Ser Ser Ser Phe Cys Leu Leu Ala Cys Leu Cys Ser Ala Ser Cys
                  10                  15                  20

gcg ttt gct gag act aga ctc gga ggg aac ttt gtt cct cca att acg   210
Ala Phe Ala Glu Thr Arg Leu Gly Gly Asn Phe Val Pro Pro Ile Thr
              25                  30                  35

aat cag ggt gaa gag atc tta ctc act tca gat ttt gtt tgt tca aac   258
Asn Gln Gly Glu Glu Ile Leu Leu Thr Ser Asp Phe Val Cys Ser Asn
          40                  45                  50

ttc ttg ggg gcg agt ttt tca agt tcc ttt atc aat agt tcc agc aat   306
Phe Leu Gly Ala Ser Phe Ser Ser Ser Phe Ile Asn Ser Ser Ser Asn
      55                  60                  65

ctc tcc tta tta ggg aag ggc ctt tcc tta acg ttt acc tct tgt caa   354
Leu Ser Leu Leu Gly Lys Gly Leu Ser Leu Thr Phe Thr Ser Cys Gln
 70                  75                  80                  85

gct cct aca aat agt aac tat gcg cta ctt tct gcc gca gag act ctg   402
Ala Pro Thr Asn Ser Asn Tyr Ala Leu Leu Ser Ala Ala Glu Thr Leu
                  90                  95                 100

acc ttc aag aat ttt tct tct ata aac ttt aca ggg aac caa tcg aca   450
Thr Phe Lys Asn Phe Ser Ser Ile Asn Phe Thr Gly Asn Gln Ser Thr
             105                 110                 115

gga ctt ggc ggc ctc atc tac gga aaa gat att gtt ttc caa tct atc   498
Gly Leu Gly Gly Leu Ile Tyr Gly Lys Asp Ile Val Phe Gln Ser Ile
         120                 125                 130

aaa gat ttg atc ttc act acg aac cgt gtt gcc tat tct cca gca tct   546
Lys Asp Leu Ile Phe Thr Thr Asn Arg Val Ala Tyr Ser Pro Ala Ser
     135                 140                 145

gta act acg tcg gca act ccc gca atc act aca gta act aca gga gcc   594
Val Thr Thr Ser Ala Thr Pro Ala Ile Thr Thr Val Thr Thr Gly Ala
150                 155                 160                 165

tct gct ctc caa cct aca gac tca ctc act gtc gaa aac ata tcc caa   642
Ser Ala Leu Gln Pro Thr Asp Ser Leu Thr Val Glu Asn Ile Ser Gln
Ser Ala Leu Gln Pro Thr Asp Ser Leu Thr Val Glu Asn Ile Ser Gln
                  170 ..              175                 180

tcg atc aag ttc ttt ggg aac ctt gcc aac ttc ggc tct gca att agc   690
Ser Ile Lys Phe Phe Gly Asn Leu Ala Asn Phe Gly Ser Ala Ile Ser
Ser Ile Lys Phe Phe Gly Asn Leu Ala Asn Phe Gly Ser Ala Ile Ser
             185                 190                 195
```

Fig. 25 (con't)

```
agt tct ccc acg gca gtc gtt aaa ttc atc aat aac acc gct acc atg   738
Ser Ser Pro Thr Ala Val Val Lys Phe Ile Asn Asn Thr Ala Thr Met
Ser Ser Pro Thr Ala Val Val Lys Phe Ile Asn Asn Thr Ala Thr Met
        200                 205                 210

agc ttc tcc cat aac ttt act tcg tca gga ggc ggc gtg att tat gga   786
Ser Phe Ser His Asn Phe Thr Ser Ser Gly Gly Gly Val Ile Tyr Gly
Ser Phe Ser His Asn Phe Thr Ser Ser Gly Gly Gly Val Ile Tyr Gly
    215                 220                 225

gga agc tct ctc ctt ttt gaa aac aat tct gga tgc atc atc ttc acc   834
Gly Ser Ser Leu Leu Phe Glu Asn Asn Ser Gly Cys Ile Ile Phe Thr
Gly Ser Ser Leu Leu Phe Glu Asn Asn Ser Gly Cys Ile Ile Phe Thr
230                 235                 240                 245

gcc aac tcc tgt gtg aac agc tta aaa ggc gtc acc cct tca tca gga   882
Ala Asn Ser Cys Val Asn Ser Leu Lys Gly Val Thr Pro Ser Ser Gly
Ala Asn Ser Cys Val Asn Ser Leu Lys Gly Val Thr Pro Ser Ser Gly
                250                 255                 260

acc tat gct tta gga agt ggc gga gcc atc tgc atc cct acg gga act   930
Thr Tyr Ala Leu Gly Ser Gly Gly Ala Ile Cys Ile Pro Thr Gly Thr
Thr Tyr Ala Leu Gly Ser Gly Gly Ala Ile Cys Ile Pro Thr Gly Thr
            265                 270                 275

ttc gaa tta aaa aac aat cag ggg aag tgc acc ttc tct tat aat ggt   978
Phe Glu Leu Lys Asn Asn Gln Gly Lys Cys Thr Phe Ser Tyr Asn Gly
Phe Glu Leu Lys Asn Asn Gln Gly Lys Cys Thr Phe Ser Tyr Asn Gly
        280                 285                 290

aca cca aat gat gcg ggt gcg atc tac gcc gaa acc tgc aac atc gta   1026
Thr Pro Asn Asp Ala Gly Ala Ile Tyr Ala Glu Thr Cys Asn Ile Val
Thr Pro Asn Asp Ala Gly Ala Ile Tyr Ala Glu Thr Cys Asn Ile Val
    295                 300                 305

ggg aac cag ggt gcc ttg ctc cta gat agc aac act gca gcg aga aat   1074
Gly Asn Gln Gly Ala Leu Leu Leu Asp Ser Asn Thr Ala Ala Arg Asn
Gly Asn Gln Gly Ala Leu Leu Leu Asp Ser Asn Thr Ala Ala Arg Asn
310                 315                 320                 325

ggc gga gcc atc tgt gct aaa gtg ctc aat att caa gga cgc ggt cct   1122
Gly Gly Ala Ile Cys Ala Lys Val Leu Asn Ile Gln Gly Arg Gly Pro
Gly Gly Ala Ile Cys Ala Lys Val Leu Asn Ile Gln Gly Arg Gly Pro
                330                 335                 340

att gaa ttc tct aga aac cgc gcg gag aag ggt gga gct att ttc ata   1170
Ile Glu Phe Ser Arg Asn Arg Ala Glu Lys Gly Gly Ala Ile Phe Ile
Ile Glu Phe Ser Arg Asn Arg Ala Glu Lys Gly Gly Ala Ile Phe Ile
            345                 350                 355

ggc ccc tct gtt gga gac cct gcg aag caa aca tcg aca ctt acg att   1218
Gly Pro Ser Val Gly Asp Pro Ala Lys Gln Thr Ser Thr Leu Thr Ile
Gly Pro Ser Val Gly Asp Pro Ala Lys Gln Thr Ser Thr Leu Thr Ile
        360                 365                 370

ttg gct tcc gaa ggt gat att gcg ttc caa gga aac atg ctc aat aca   1266
Leu Ala Ser Glu Gly Asp Ile Ala Phe Gln Gly Asn Met Leu Asn Thr
Leu Ala Ser Glu Gly Asp Ile Ala Phe Gln Gly Asn Met Leu Asn Thr
    375                 380                 385
```

Fig. 25 (con't)

```
aaa cct gga atc cgc aat gcc atc act gta gaa gca ggg gga gag att   1314
Lys Pro Gly Ile Arg Asn Ala Ile Thr Val Glu Ala Gly Gly Glu Ile
Lys Pro Gly Ile Arg Asn Ala Ile Thr Val Glu Ala Gly Gly Glu Ile
390                 395                 400                 405

gtg tct cta tct gca caa gga ggc tca cgt ctt gta ttt tat gat ccc   1362
Val Ser Leu Ser Ala Gln Gly Gly Ser Arg Leu Val Phe Tyr Asp Pro
Val Ser Leu Ser Ala Gln Gly Gly Ser Arg Leu Val Phe Tyr Asp Pro
                410                 415                 420

att aca cat agc ctc cca acc aca agt ccg tct aat aaa gac att aca   1410
Ile Thr His Ser Leu Pro Thr Thr Ser Pro Ser Asn Lys Asp Ile Thr
Ile Thr His Ser Leu Pro Thr Thr Ser Pro Ser Asn Lys Asp Ile Thr
            425                 430                 435

atc aac gct aat ggc gct tca gga tct gta gtc ttt aca agt aag gga   1458
Ile Asn Ala Asn Gly Ala Ser Gly Ser Val Val Phe Thr Ser Lys Gly
Ile Asn Ala Asn Gly Ala Ser Gly Ser Val Val Phe Thr Ser Lys Gly
        440                 445                 450

ctc tcc tct aca gaa ctc ctg ttg cct gcc aac acg aca act ata ctt   1506
Leu Ser Ser Thr Glu Leu Leu Leu Pro Ala Asn Thr Thr Thr Ile Leu
Leu Ser Ser Thr Glu Leu Leu Leu Pro Ala Asn Thr Thr Thr Ile Leu
    455                 460                 465

cta gga aca gtc aag atc gct agt gga gaa ctg aag att act gac aat   1554
Leu Gly Thr Val Lys Ile Ala Ser Gly Glu Leu Lys Ile Thr Asp Asn
Leu Gly Thr Val Lys Ile Ala Ser Gly Glu Leu Lys Ile Thr Asp Asn
470                 475                 480                 485

gcg gtt gtc aat gtt gct ggc ttc gct act cag ggc tca ggt cag ctt   1602
Ala Val Val Asn Val Ala Gly Phe Ala Thr Gln Gly Ser Gly Gln Leu
Ala Val Val Asn Val Ala Gly Phe Ala Thr Gln Gly Ser Gly Gln Leu
                490                 495                 500

acc ctg ggc tct gga gga acc tta ggg ctg gca aca ccc acg gga gca   1650
Thr Leu Gly Ser Gly Gly Thr Leu Gly Leu Ala Thr Pro Thr Gly Ala
Thr Leu Gly Ser Gly Gly Thr Leu Gly Leu Ala Thr Pro Thr Gly Ala
            505                 510                 515

cct gcc gct gta gac ttt acg att gga aag tta gca ttc gat cct ttt   1698
Pro Ala Ala Val Asp Phe Thr Ile Gly Lys Leu Ala Phe Asp Pro Phe
Pro Ala Ala Val Asp Phe Thr Ile Gly Lys Leu Ala Phe Asp Pro Phe
        520                 525                 530

tcc ttc cta aaa aga gat ttt gtt tca gca tca gta aat gca ggc aca   1746
Ser Phe Leu Lys Arg Asp Phe Val Ser Ala Ser Val Asn Ala Gly Thr
Ser Phe Leu Lys Arg Asp Phe Val Ser Ala Ser Val Asn Ala Gly Thr
    535                 540                 545

aaa aac gtc act tta aca gga gct ctg gtt ctt gat gaa cat gac gtt   1794
Lys Asn Val Thr Leu Thr Gly Ala Leu Val Leu Asp Glu His Asp Val
Lys Asn Val Thr Leu Thr Gly Ala Leu Val Leu Asp Glu His Asp Val
550                 555                 560                 565

aca gat ctt tat gat atg gtg tca tta caa tct cca gta gca att cct   1842
Thr Asp Leu Tyr Asp Met Val Ser Leu Gln Ser Pro Val Ala Ile Pro
Thr Asp Leu Tyr Asp Met Val Ser Leu Gln Ser Pro Val Ala Ile Pro
                570                 575                 580
```

Fig. 25 (con't)

```
atc gct gtt ttc aaa gga gca acc gtt act aag aca gga ttt cct gat   1890
Ile Ala Val Phe Lys Gly Ala Thr Val Thr Lys Thr Gly Phe Pro Asp
Ile Ala Val Phe Lys Gly Ala Thr Val Thr Lys Thr Gly Phe Pro Asp
            585                 590                 595

ggg gag att gcg act cca agc cac tac ggc tac caa gga aag tgg tcc   1938
Gly Glu Ile Ala Thr Pro Ser His Tyr Gly Tyr Gln Gly Lys Trp Ser
Gly Glu Ile Ala Thr Pro Ser His Tyr Gly Tyr Gln Gly Lys Trp Ser
        600                 605                 610

tac aca tgg tcc cgt ccc ctg tta att cca gct cct gat gga gga ttt   1986
Tyr Thr Trp Ser Arg Pro Leu Leu Ile Pro Ala Pro Asp Gly Gly Phe
Tyr Thr Trp Ser Arg Pro Leu Leu Ile Pro Ala Pro Asp Gly Gly Phe
    615                 620                 625

cct gga ggt ccc tct cct agc gca aat act ctc tat gct gta tgg aat   2034
Pro Gly Gly Pro Ser Pro Ser Ala Asn Thr Leu Tyr Ala Val Trp Asn
Pro Gly Gly Pro Ser Pro Ser Ala Asn Thr Leu Tyr Ala Val Trp Asn
630                 635                 640                 645

tca gac act ctc gtg cgt tct acc tat atc tta gat ccc gag cgt tac   2082
Ser Asp Thr Leu Val Arg Ser Thr Tyr Ile Leu Asp Pro Glu Arg Tyr
Ser Asp Thr Leu Val Arg Ser Thr Tyr Ile Leu Asp Pro Glu Arg Tyr
                650                 655                 660

gga gaa att gtc agc aac agc tta tgg att tcc ttc tta gga aat cag   2130
Gly Glu Ile Val Ser Asn Ser Leu Trp Ile Ser Phe Leu Gly Asn Gln
Gly Glu Ile Val Ser Asn Ser Leu Trp Ile Ser Phe Leu Gly Asn Gln
            665                 670                 675

gca ttc tct gat att ctc caa gat gtt ctt ttg ata gat cat ccc ggg   2178
Ala Phe Ser Asp Ile Leu Gln Asp Val Leu Leu Ile Asp His Pro Gly
Ala Phe Ser Asp Ile Leu Gln Asp Val Leu Leu Ile Asp His Pro Gly
        680                 685                 690

ttg tcc ata acc gcg aaa gct tta gga gcc tat gtc gaa cac aca cca   2226
Leu Ser Ile Thr Ala Lys Ala Leu Gly Ala Tyr Val Glu His Thr Pro
Leu Ser Ile Thr Ala Lys Ala Leu Gly Ala Tyr Val Glu His Thr Pro
    695                 700                 705

aga caa gga cat gag ggc ttt tca ggt cgc tat gga ggc tac caa gct   2274
Arg Gln Gly His Glu Gly Phe Ser Gly Arg Tyr Gly Gly Tyr Gln Ala
Arg Gln Gly His Glu Gly Phe Ser Gly Arg Tyr Gly Gly Tyr Gln Ala
710                 715                 720                 725

gcg cta tct atg aac tac acg gac cac act acg tta gga ctt tct ttc   2322
Ala Leu Ser Met Asn Tyr Thr Asp His Thr Thr Leu Gly Leu Ser Phe
Ala Leu Ser Met Asn Tyr Thr Asp His Thr Thr Leu Gly Leu Ser Phe
                730                 735                 740

ggg cag ctt tat gga aaa act aac gcc aac ccc tac gat tca cgt tgc   2370
Gly Gln Leu Tyr Gly Lys Thr Asn Ala Asn Pro Tyr Asp Ser Arg Cys
Gly Gln Leu Tyr Gly Lys Thr Asn Ala Asn Pro Tyr Asp Ser Arg Cys
            745                 750                 755

tca gaa caa atg tat tta ctc tcg ttc ttt ggt caa ttc cct atc gtg   2418
Ser Glu Gln Met Tyr Leu Leu Ser Phe Phe Gly Gln Phe Pro Ile Val
Ser Glu Gln Met Tyr Leu Leu Ser Phe Phe Gly Gln Phe Pro Ile Val
        760                 765                 770
```

Fig. 25 (con't)

```
act caa aag agc gag gcc tta att tcc tgg aaa gca gct tat ggt tat   2466
Thr Gln Lys Ser Glu Ala Leu Ile Ser Trp Lys Ala Ala Tyr Gly Tyr
Thr Gln Lys Ser Glu Ala Leu Ile Ser Trp Lys Ala Ala Tyr Gly Tyr
    775                 780                 785

tcc aaa aat cac cta aat acc acc tac ctc aga cct gac aaa gct cca   2514
Ser Lys Asn His Leu Asn Thr Thr Tyr Leu Arg Pro Asp Lys Ala Pro
Ser Lys Asn His Leu Asn Thr Thr Tyr Leu Arg Pro Asp Lys Ala Pro
790                 795                 800                 805

aaa tct caa ggg caa tgg cat aac aat agt tac tat gtt ctt att tct   2562
Lys Ser Gln Gly Gln Trp His Asn Asn Ser Tyr Tyr Val Leu Ile Ser
Lys Ser Gln Gly Gln Trp His Asn Asn Ser Tyr Tyr Val Leu Ile Ser
                810                 815                 820

gca gaa cat cct ttc cta aac tgg tgt ctt ctt aca aga cct ctg gct   2610
Ala Glu His Pro Phe Leu Asn Trp Cys Leu Leu Thr Arg Pro Leu Ala
Ala Glu His Pro Phe Leu Asn Trp Cys Leu Leu Thr Arg Pro Leu Ala
            825                 830                 835

caa gct tgg gat ctt tca ggt ttt att tcc gca gaa ttc cta ggt ggt   2658
Gln Ala Trp Asp Leu Ser Gly Phe Ile Ser Ala Glu Phe Leu Gly Gly
Gln Ala Trp Asp Leu Ser Gly Phe Ile Ser Ala Glu Phe Leu Gly Gly
        840                 845                 850

tgg caa agt aag ttc aca gaa act gga gat ctg caa cgt agc ttt agt   2706
Trp Gln Ser Lys Phe Thr Glu Thr Gly Asp Leu Gln Arg Ser Phe Ser
Trp Gln Ser Lys Phe Thr Glu Thr Gly Asp Leu Gln Arg Ser Phe Ser
    855                 860                 865

aga ggt aaa ggg tac aat gtt tcc cta ccg ata gga tgt tct tct caa   2754
Arg Gly Lys Gly Tyr Asn Val Ser Leu Pro Ile Gly Cys Ser Ser Gln
Arg Gly Lys Gly Tyr Asn Val Ser Leu Pro Ile Gly Cys Ser Ser Gln
870                 875                 880                 885

tgg ttc aca cca ttt aag aag gct cct tct aca ctg acc atc aaa ctt   2802
Trp Phe Thr Pro Phe Lys Lys Ala Pro Ser Thr Leu Thr Ile Lys Leu
Trp Phe Thr Pro Phe Lys Lys Ala Pro Ser Thr Leu Thr Ile Lys Leu
                890                 895                 900

gcc tac aag cct gat atc tat cgt gtc aac cct cac aat att gtg act   2850
Ala Tyr Lys Pro Asp Ile Tyr Arg Val Asn Pro His Asn Ile Val Thr
Ala Tyr Lys Pro Asp Ile Tyr Arg Val Asn Pro His Asn Ile Val Thr
            905                 910                 915

gtc gtc tca aac caa gag agc act tcg atc tca gga gca aat cta cgc   2898
Val Val Ser Asn Gln Glu Ser Thr Ser Ile Ser Gly Ala Asn Leu Arg
Val Val Ser Asn Gln Glu Ser Thr Ser Ile Ser Gly Ala Asn Leu Arg
        920                 925                 930

cgc cac ggt ttg ttt gta caa atc cat gat gta gta gat ctc acc gag   2946
Arg His Gly Leu Phe Val Gln Ile His Asp Val Val Asp Leu Thr Glu
Arg His Gly Leu Phe Val Gln Ile His Asp Val Val Asp Leu Thr Glu
    935                 940                 945
```

Fig. 25 (con't)

```
gac act cag gcc ttt cta aac tat acc ttt gac ggg aaa aat gga ttt   2994
Asp Thr Gln Ala Phe Leu Asn Tyr Thr Phe Asp Gly Lys Asn Gly Phe
Asp Thr Gln Ala Phe Leu Asn Tyr Thr Phe Asp Gly Lys Asn Gly Phe
950                 955                 960                 965

aca aac cac cga gtg tct aca gga cta aaa tcc aca ttt taaaactcta   3043
Thr Asn His Arg Val Ser Thr Gly Leu Lys Ser Thr Phe
Thr Asn His Arg Val Ser Thr Gly Leu Lys Ser Thr Phe
                970                 975

agctctgctt agagttttct gtagccccgg tcgtcttaga atcctctatc catcatcgaa 3103

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Figure 26 (RY-47)

Restriction enzyme analysis of CPN100630

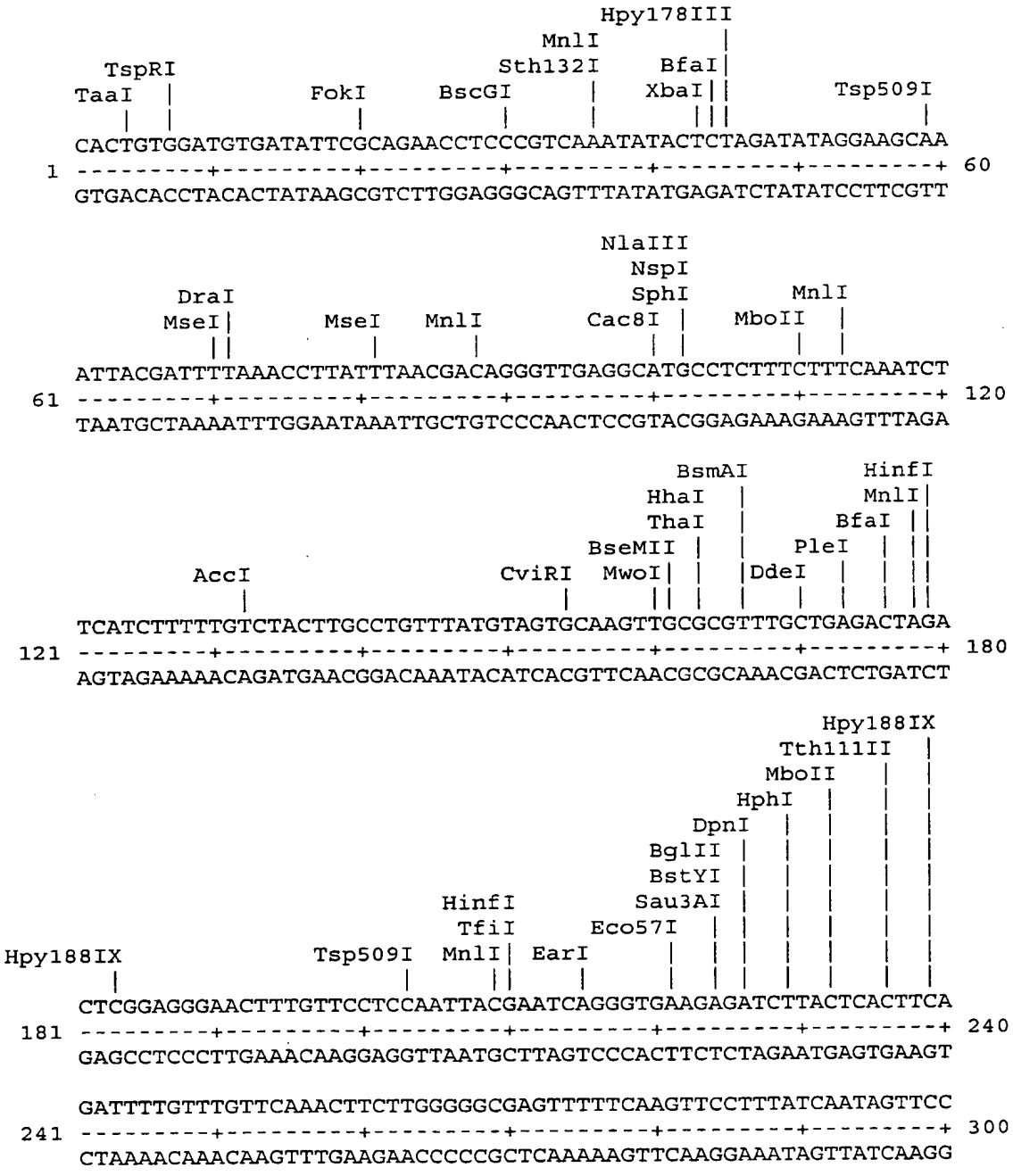
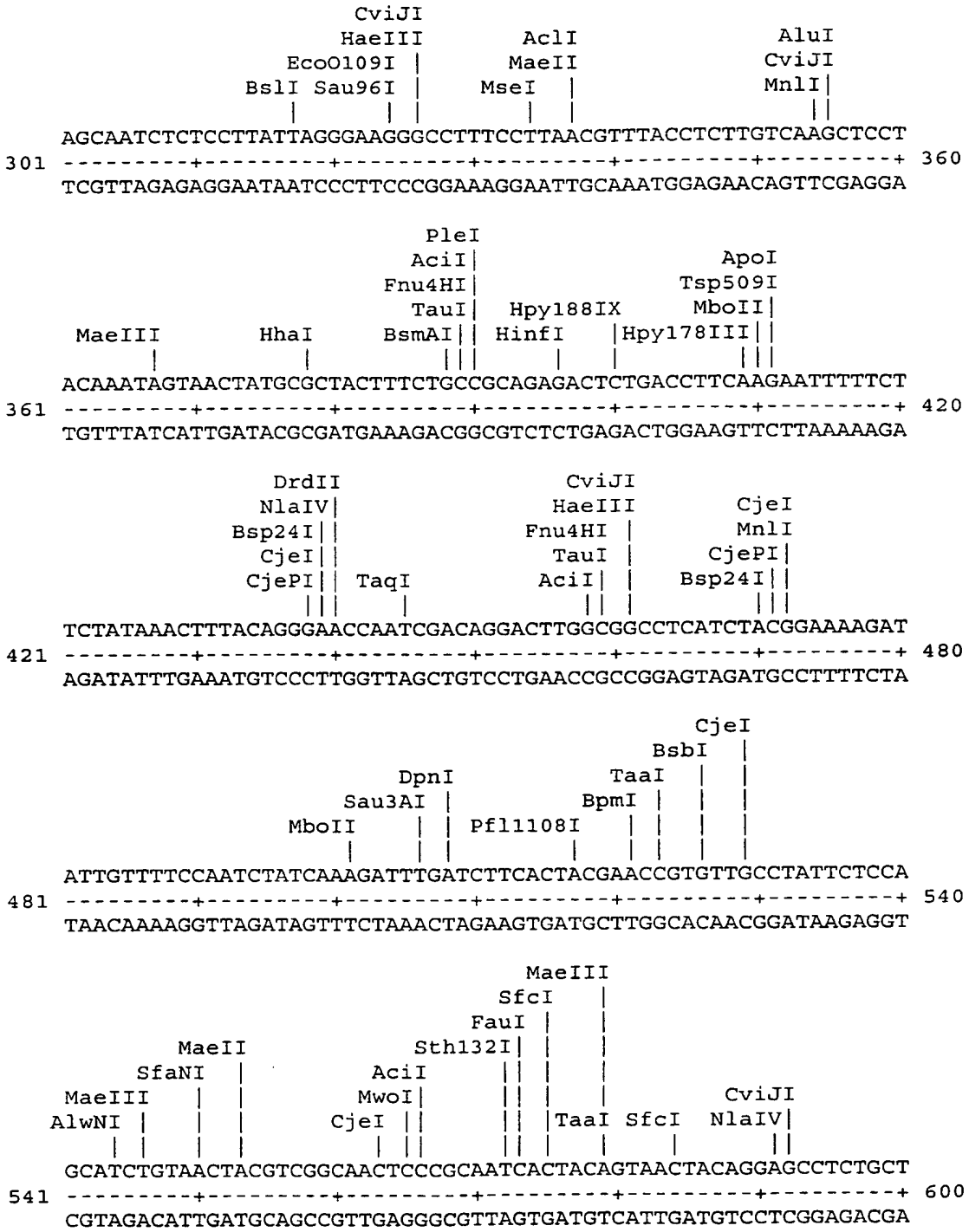


Fig. 26 (con't)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AciI
ApoI
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Tsp509I
TauI
Hpy188IX
MboII
MaeIII
HhaI
BsmAI
HinfI
Hpy178III
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HaeIII
CjeI
Bsp24I
Fnu4HI
MnlI
CjeI
TauI
CjePI
CjePI
TaqI
AciI
Bsp24I
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CjeI
BsbI
DpnI
TaaI
Sau3AI
BpmI
MboII
Pfl1108I
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540
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SfcI
FauI
MaeII
Sth132I
SfaNI
AciI
MaeIII
MwoI
CviJI
AlwNI
CjeI
TaaI
SfcI
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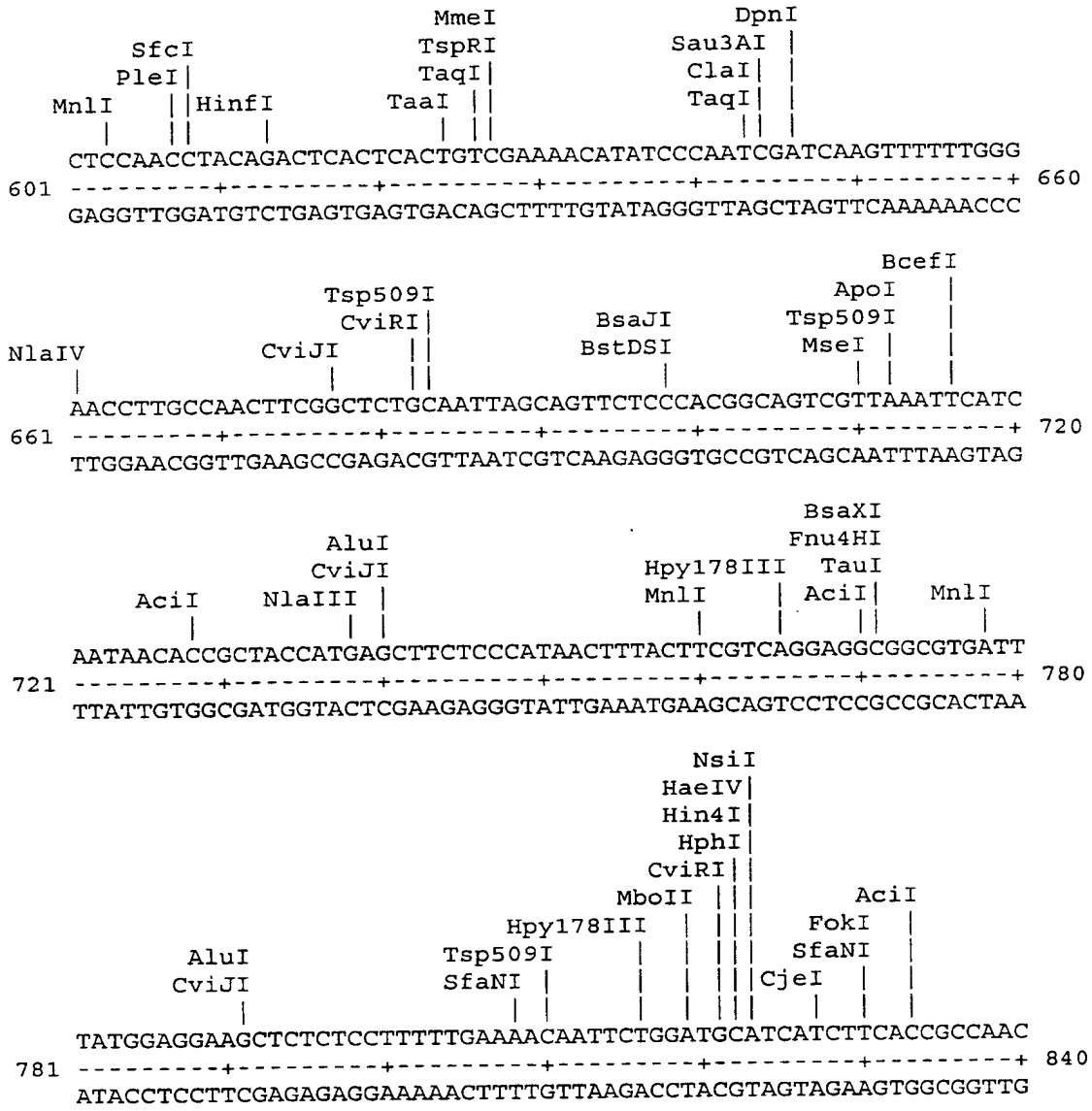
Fig. 26 (con't)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ApoI
CviRI
BsaJI
Tsp509I
NlaIV
CviJI
BstDSI
MseI
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BsaXI
AluI
Fnu4HI
CviJI
Hpy178III
TauI
AciI
NlaIII
MnlI
AciI
MnlI
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Hin4I
HphI
CviRI
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AluI
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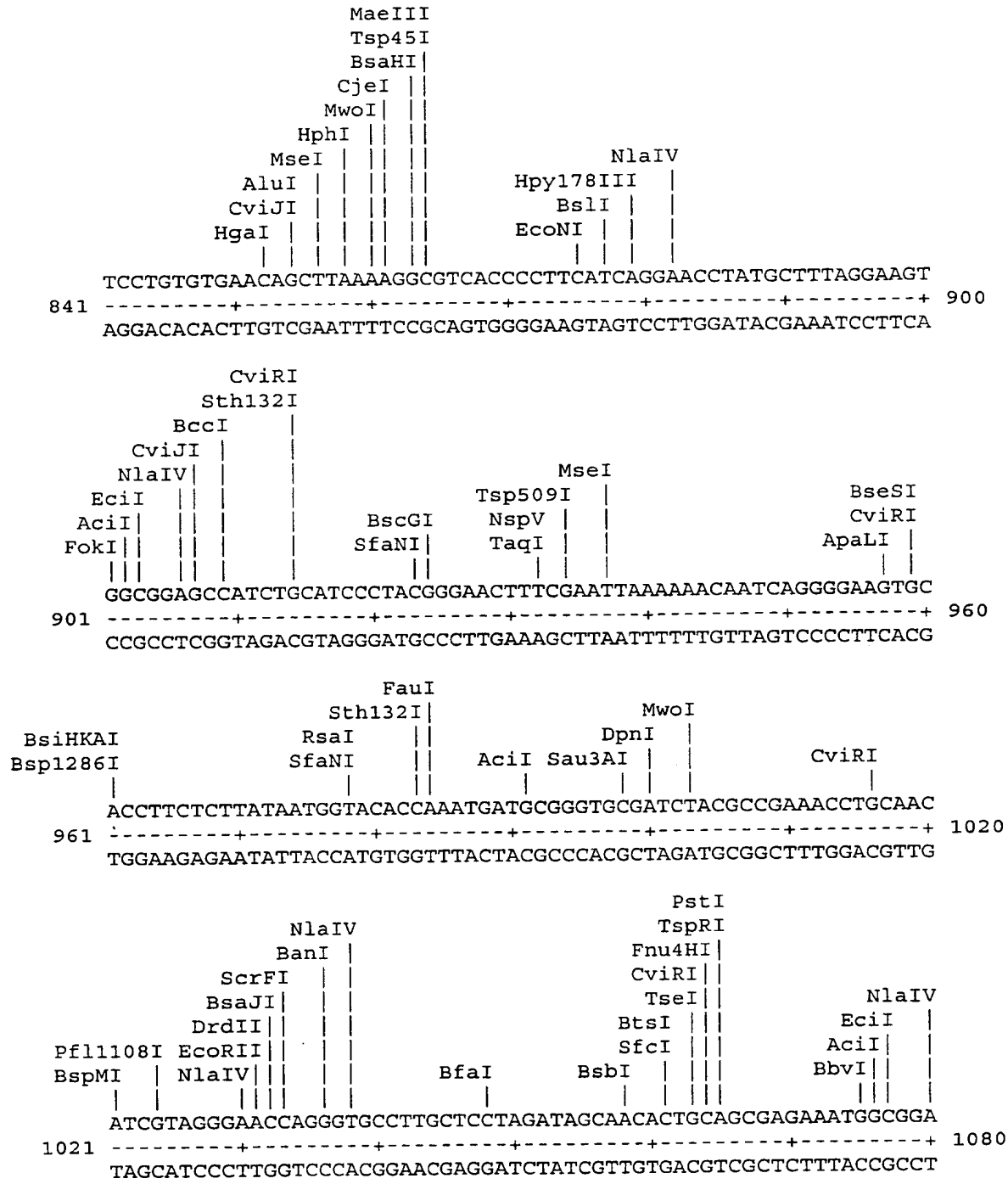
Fig. 26 (con't)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BccI
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BanI
ScrFI
BsaJI
DrdII
Fnu4HI
CviRI
TseI
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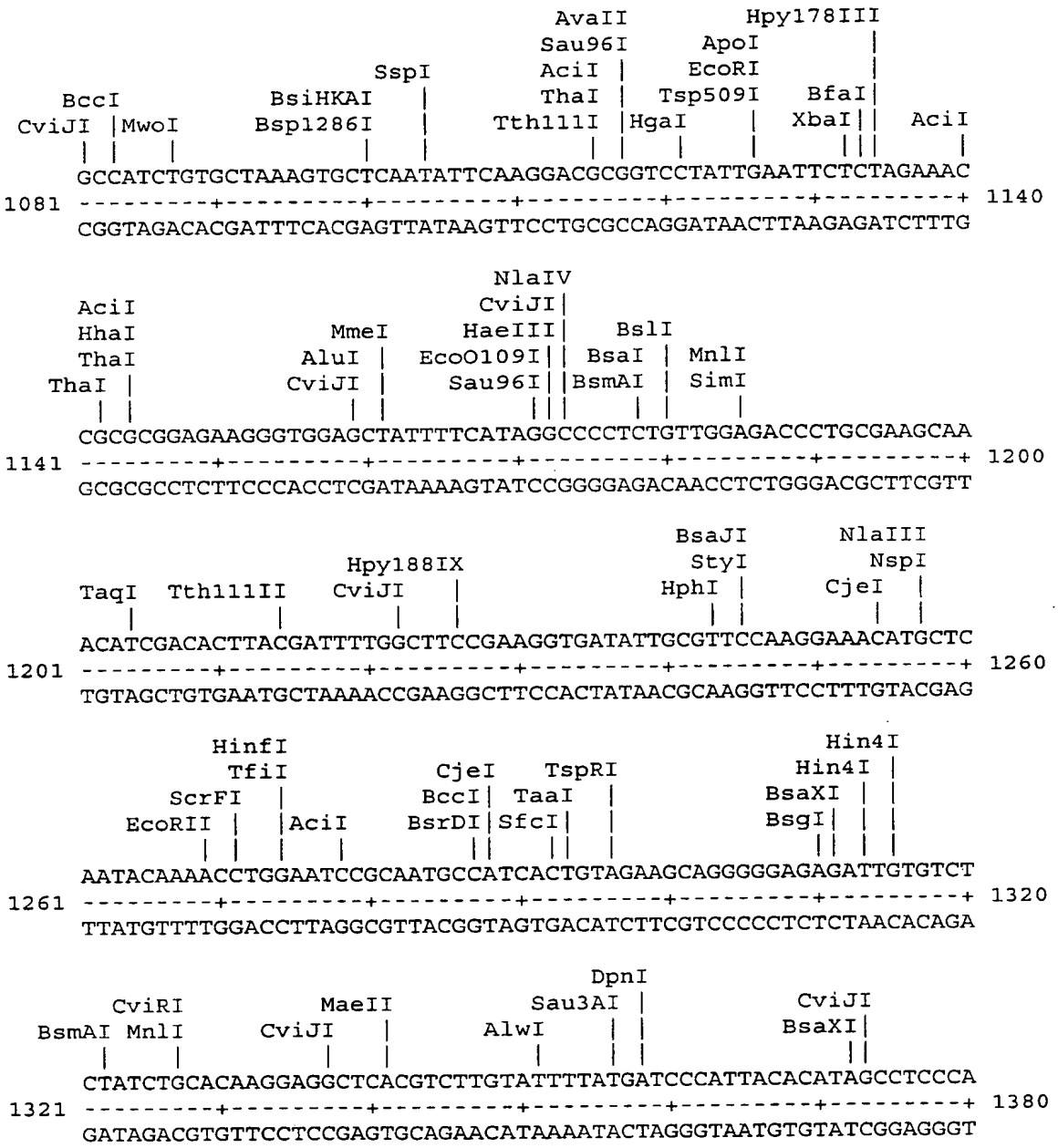
Fig. 26 (con't)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HgaI
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ThaI
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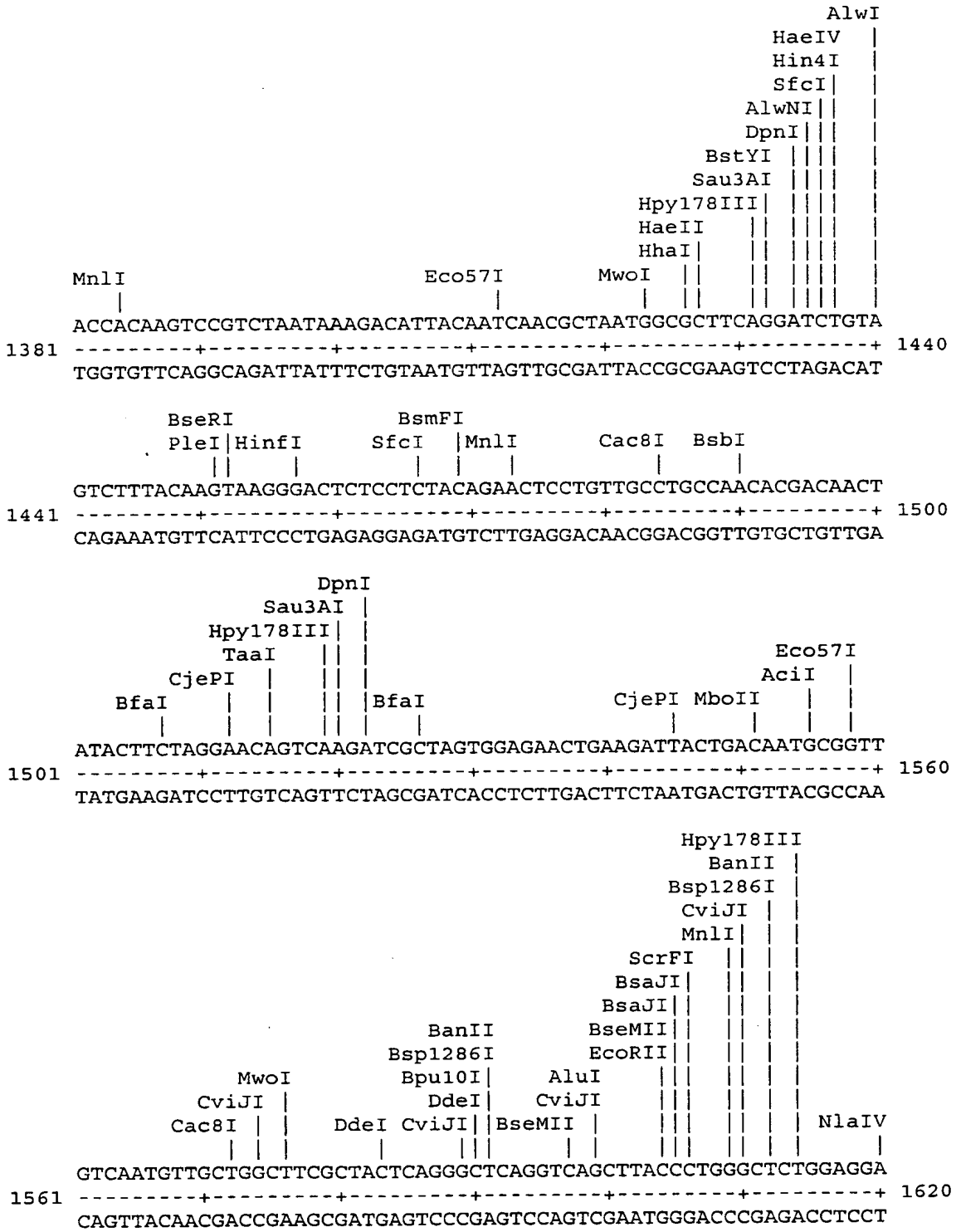
Fig. 26 (con't)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BseRI
PleI
HinfI
BsmFI
SfcI
MnlI
Cac8I
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1441 + 1500
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CviJI
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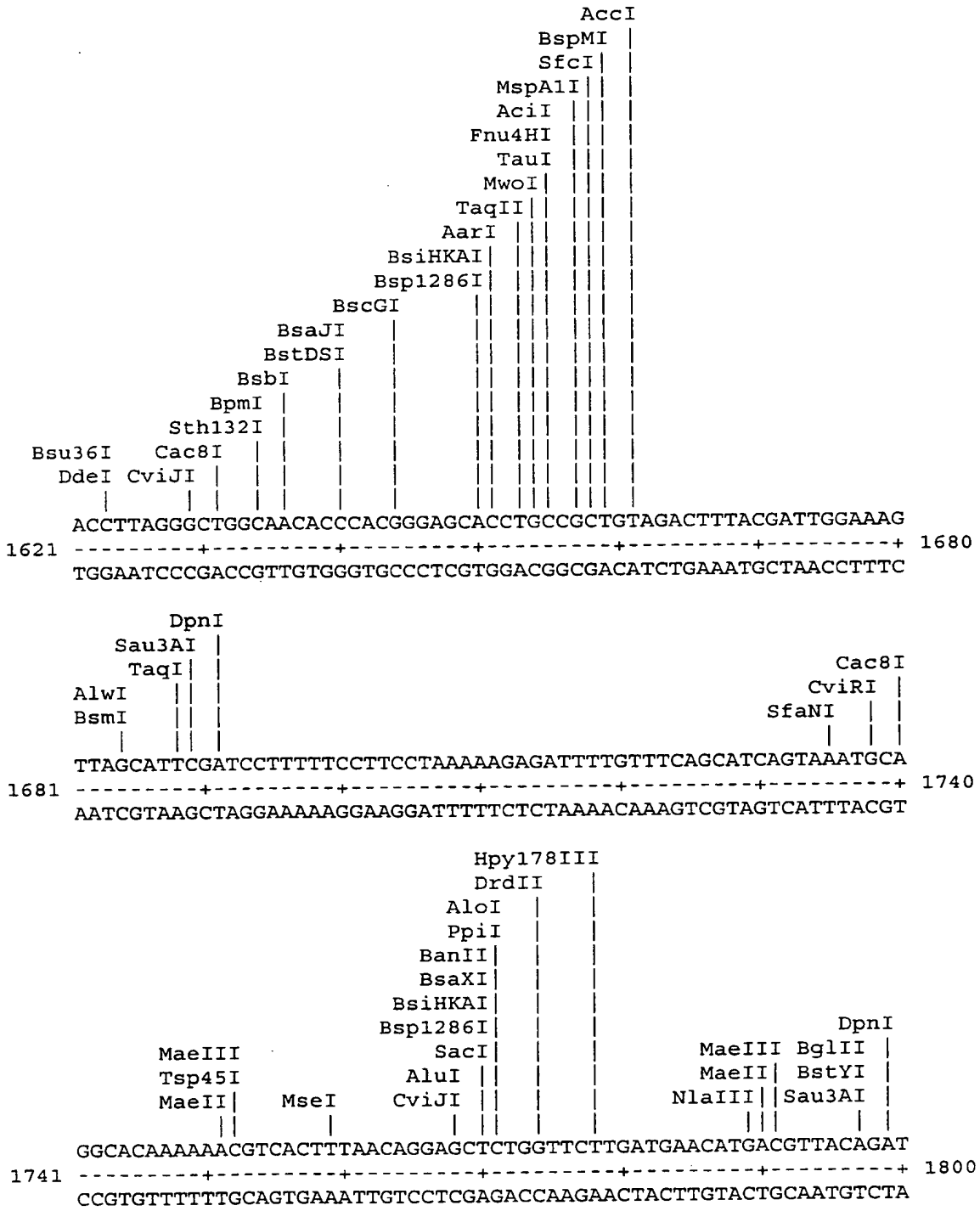
Fig. 26 (con't)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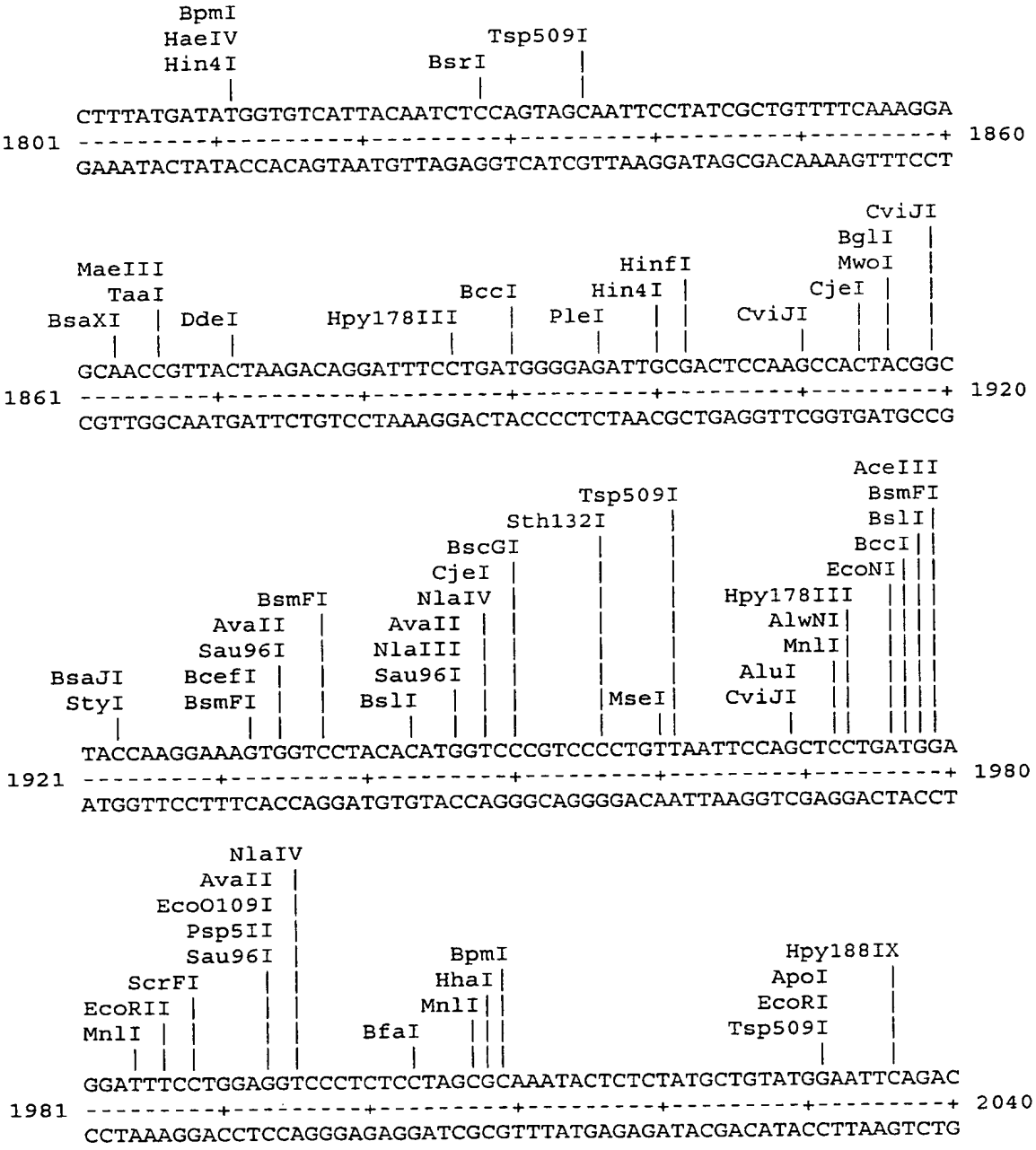
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Fig. 26 (con't)

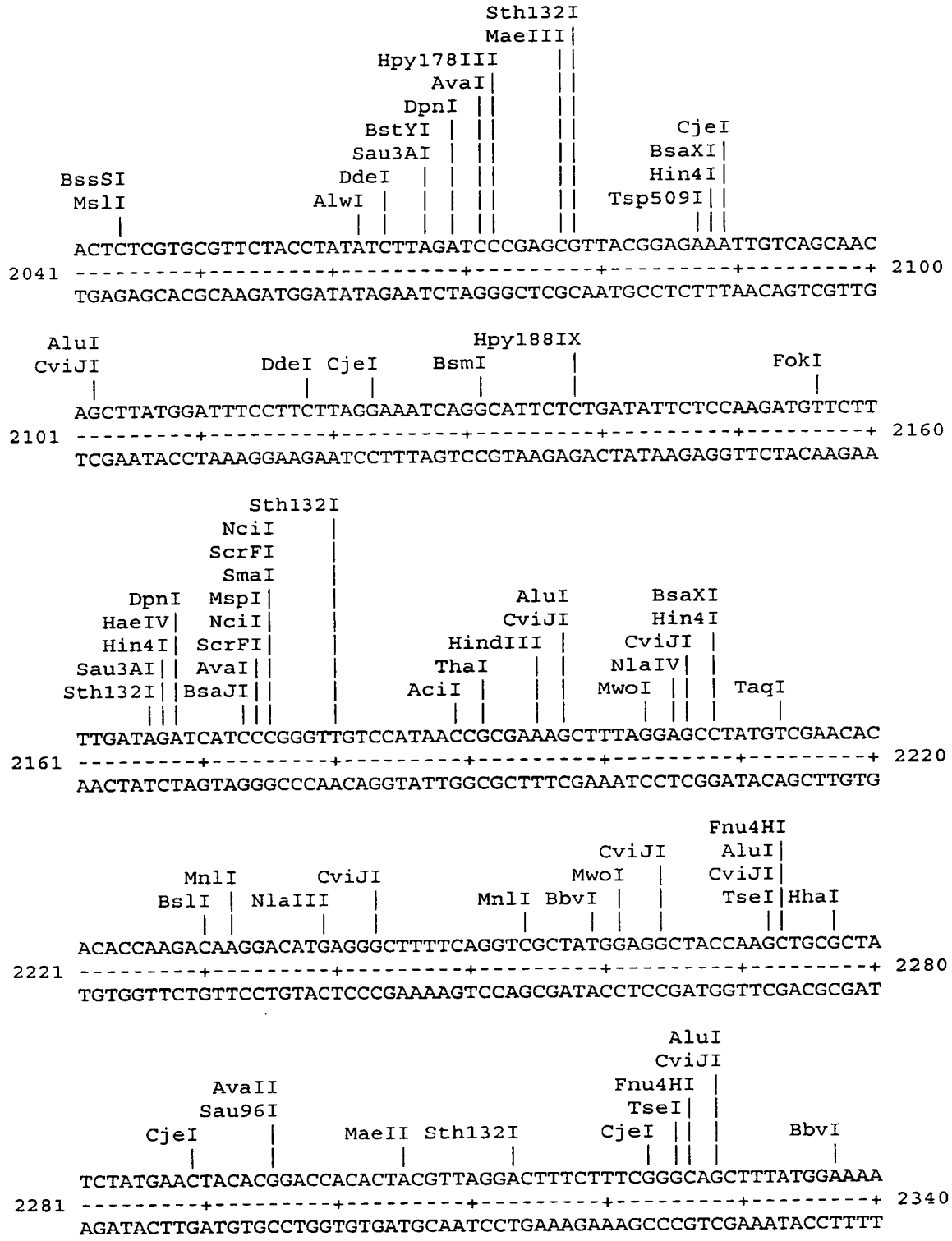
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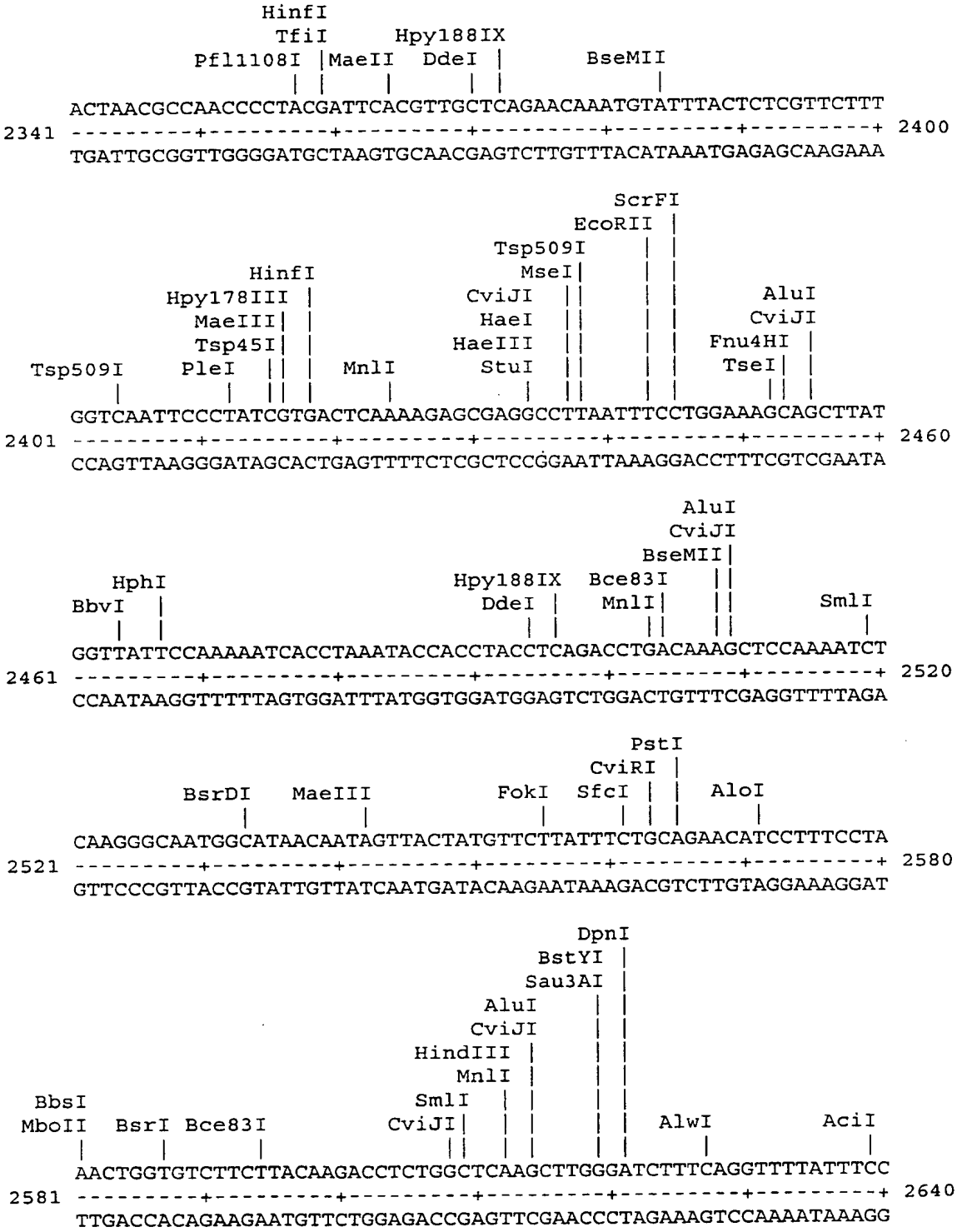
Fig. 26 (con't)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2521
2580
GTTCCCGTTACCGTATTGTTATCAATGATACAAGAATAAAGACGTCTTGTAGGAAAGGAT
DpnI
BstYI
Sau3AI
AluI
CviJI
HindIII
MnlI
BbsI
SmlI
MboII
BsrI
Bce83I
CviJI
AlwI
AciI
AACTGGTGTCTTCTTACAAGACCTCTGGCTCAAGCTTGGGATCTTTCAGGTTTTATTTCC
2581
2640
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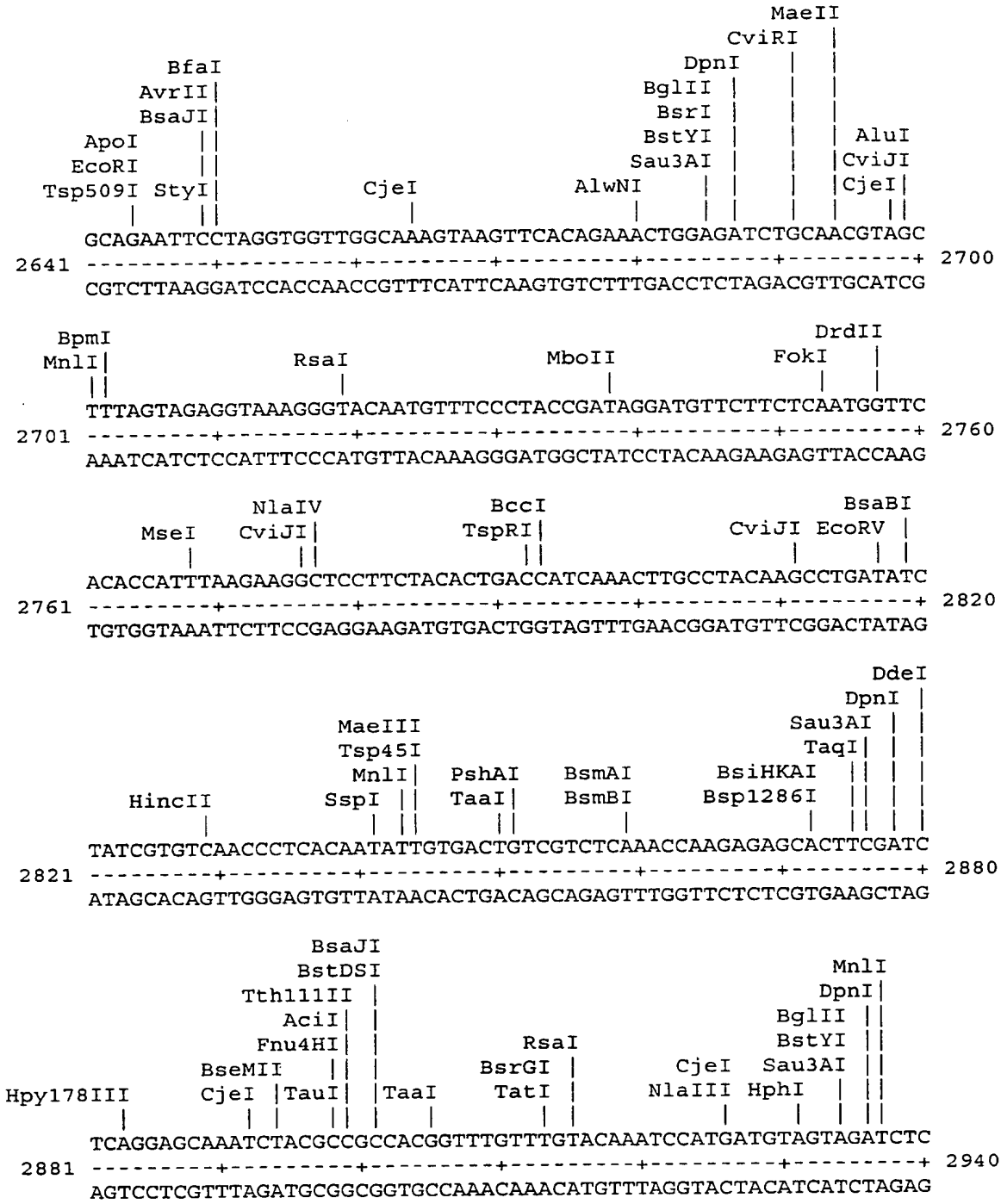
Fig. 26 (con't)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AluI
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BfaI
AvrII
BsaJI
ApoI
EcoRI
Tsp509I
StyI
CjeI
AlwNI
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2700
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MnlI
RsaI
MboII
DrdII
FokI
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NlaIV
CviJI
BccI
TspRI
BsaBI
MseI
CviJI
EcoRV
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DdeI
DpnI
MaeIII
Tsp45I
Sau3AI
TaqI
MnlI
PshAI
BsmAI
BsiHKAI
HincII
SspI
TaaI
BsmBI
Bsp1286I
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2880
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BsaJI
BstDSI
Tth111II
AciI
Fnu4HI
MnlI
DpnI
BglII
BstYI
RsaI
BseMII
BsrGI
CjeI
Sau3AI
Hpy178III
CjeI
TauI
TaaI
TatI
NlaIII
HphI
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2940
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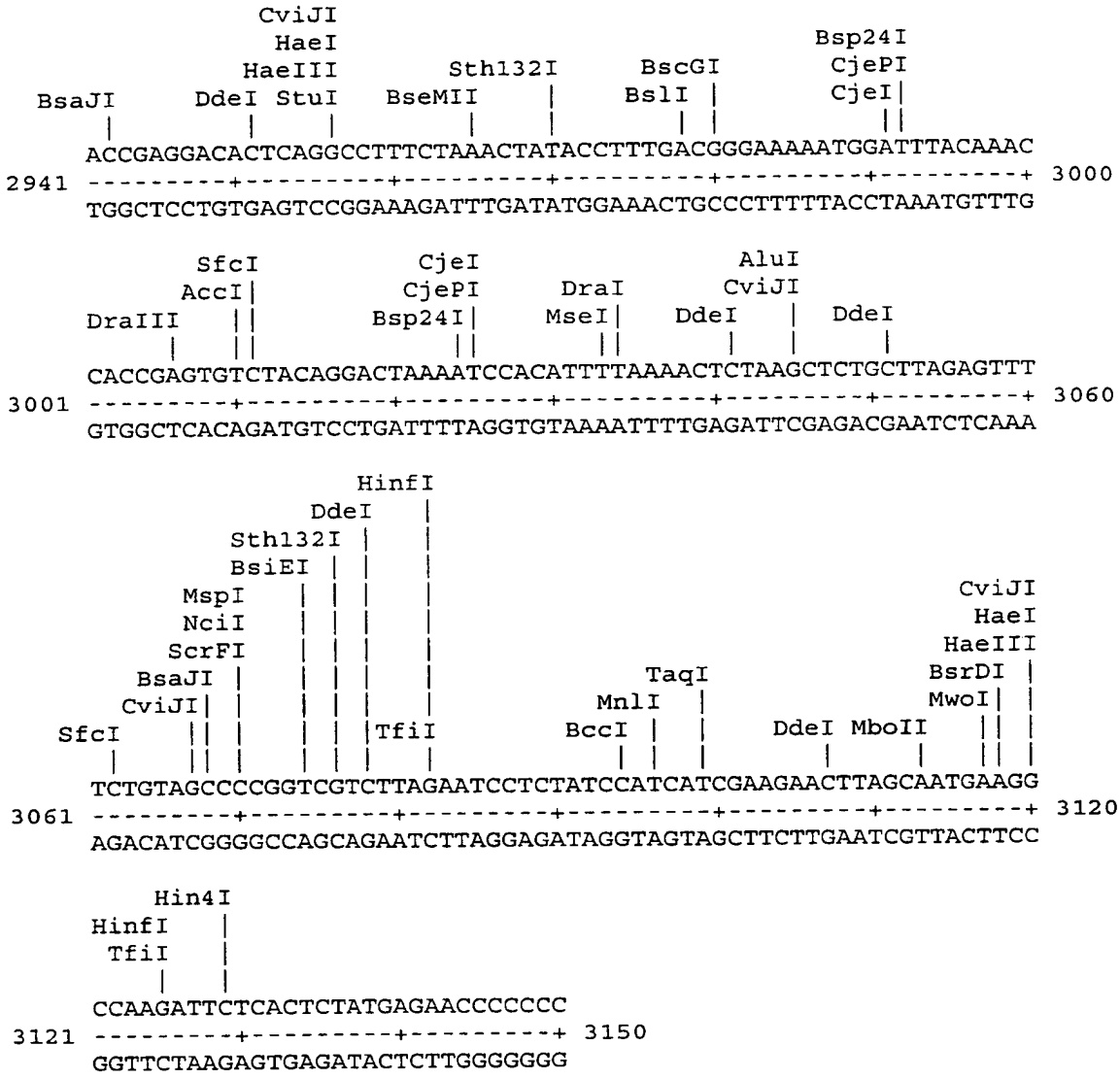
Fig. 26 (con't)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DraIII
CjeI
CjePI
Bsp24I
DraI
MseI
AluI
CviJI
DdeI
DdeI
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HinfI
DdeI
Sth132I
BsiEI
MspI
NciI
ScrFI
BsaJI
CviJI
SfcI
TfiI
TaqI
MnlI
BccI
DdeI
MboII
CviJI
HaeI
HaeIII
BsrDI
MwoI
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3120
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Hin4I
HinfI
TfiI
CCAAGATTCTCACTCTATGAGAACCCCCCC
3121
3150
GGTTCTAAGAGTGAGATACTCTTGGGGGGG

Figure 27: CPN100397

```
  1 MKIPLRFLLI SLVPTLSMSN LLGAATTEEL SASNSFDGTT STTSFSSKTS
 51 SATDGTNYVF KDSVVIENVP KTGETQSTSC FKNDAAAGDL NFLGGGFSFT
101 FSNIDATTAS GAAIGSEAAN KTVTLSGFSA LSFLKSPAST VTNGLGAINV
151 KGNLSLLDND KVLIQDNFST GDGGAINCAG SLKIANNKSL SFIGNSSSTR
201 GGAIHTKNLT LSSGGETLFQ GNTAPTAAGK GGAIAIADSG TLSISGDSGD
251 IIFEGNTIGA TGTVSHSAID LGTSAKITAL RAAQGHTIYF YDPITVTGST
301 SVADALNINS PDTGDNKEYT GTIVFSGEKL TEAEAKDEKN RTSKLLQNVA
351 FKNGTVVLKG DVVLSANGFS QDANSKLIMD LGTSLVANTE SIELTNLEIN
401 IDSLRNGKKI KLSAATAQKD IRIDRPVVLA ISDESFYQNG FLNEDHSYDG
451 ILELDAGKDI VISADSRSID AVQSPYGYQG KWTINWSTDD KKATVSWAKQ
501 SFNPTAEQEA PLVPNLLWGS FIDVRSFQNF IELGTEGAPY EKRFWVAGIS
551 NVLHRSGREN QRKFRHVSGG AVVGASTRMP GGDTLSLGFA QLFARDKDYF
601 MNTNFAKTYA GSLRLQHDAS LYSVVSILLG EGGLREILLP YVSKTLPCSF
651 YGQLSYGHTD HRMKTESLPP PPPTLSTDHT SWGGYVWAGE LGTRVAVENT
701 SGRGFFQEYT PFVKVQAVYA RQDSFVELGA ISRDFSDSHL YNLAIPLGIK
751 LEKRFAEQYY HVVAMYSPDV CRSNPKCTTT LLSNQGSWKT KGSNLARQAG
801 IVQASGFRSL GAAAELFGNF GFEWRGSSRS YNVDAGSKIK F
```

Possible T cell epitope:

516 LLWGSFIDV

Possible B cell epitope:

554 HRSGRENQRKFRHV

Figure 28: CPN100421

```
  1 MPPLNADDVL PRDHLSDGSF SDTYPDITTQ AIILIFLALS PFLVMLLTSY
 51 LKIIITLVLL RNALGVQQTP PSQVLNGIAL ILSIYVMFPT GVAMYKDARK
101 EIEANTIPQS LFTAEGAETV FVALNKSKEP LRSFLIRNTP KAQIQSFYKI
151 SQKTFPSEIR AHLTASDFVI IIPAFIMGQI KNAFEIGVLI YLPFFVIDLV
201 TANVLVAMQM MMLSPLSISL PLKLLLIVMV DGWTLLLQGL MISFK
```

Possible T cell epitope:

188 VLIYLPFFV

Possible B cell epitope:

125 NKSKEPLR

Figure 29: CPN100422

```
  1 MKFFSLIFKD DDVSPNKKVL SPEAFSAFLD AKELLEKTKA DSEAYVAETE
 51 QKCAQIRQEA KDQGFKEGSE SWSKQIAFLE EETKNLRIRV REALVPLAIA
101 SVRKIIGKEL ELHPETIVSI ISQALKELTQ NKHIIISVNP KDLPLVEKSR
151 PELKNIVEYA DSLILTAKPD VTPGGCIIET EAGIINAQLD VQLDALEKAF
201 STILKAKNPV DEPSETSSST DSSSLSNDQD KKE
```

Possible T cell epitope:

163 LILTAKPDV

Possible B cell epitope:

226 SNDQDKKE

Figure 30: CPN100424

```
  1 MTLLCCTSCN SRSLIVHGLP GREANEIVVL LVSKGVAAQK LPQAAAATAG
 51 AATEQMWDIA VPSAQITEAL AILNQAGLPR MKGTSLLDLF AKQGLVPSEL
101 QEKIRYQEGL SEQMASTIRK MDGVVDASVQ ISFTTENEDN LPLTASVYIK
151 HRGVLDNPNS IMVSKIKRLI ASAVPGLVPE NVSVVSDRAA YSDITINGPW
201 GLTEEIDYVS VWGIILAKSS LTKFRLIFYV LILILFVISC GLLWVIWKTH
251 TLIMTMGGTK GFFNPTPYTK NALEAKKAEG AAADKEKKED ADSQGESKNA
301 ETSDKDSSDK DAPEGSNEIE GA
```

Possible T cell epitope:

201 GLTEEIDYV

Possible B cell epitope:

284 DKEKKEDADSQGESKNAETSDKDSSDKDAPEGSNEIE

Figure 31: CPN100426

```
   1 MTIRVRNLAY SVNKKKILDG VTFSLERGHI TLFVGKSGSG KTMILRALAG
  51 LVQPTQGDIW IEGEAPALVF QQPELFSHMT VLGNCTHPQI HIKGRSTEEA
 101 REKAFELLHL LDIEEVAKNY PDQLSGGQKQ RVAIVRSLCM DKHTLLFDEP
 151 TSALDPFATA SFRHLLETLR DQELTVGLTT HDMQFVHSCL DRIYLIDQGT
 201 VAGVYDKRDG ELDSGHPLSK YIHSAQ
```

Possible T cell epitope:

145 LLFDEPTSA

Possible B cell epitope:

205 YDKRDGE

Figure 32: CPN100508

```
   1 MKRPFFTYLC IIFYGSCASL SLHAGLSFPE VRGATAAVVH ADSGKVFYDK
  51 DIDAVIYPAS MTKIATALFI LKHYPTVLDT LIKVKQDAIA SITPQAKKQS
 101 GYRSPPHWLE TDGSTIQLHL REELLGWDLF HALLVCSAND AANVLAMACC
 151 GSVEKFMDKL NFFLKEEIGC THTHFNNPHG LHHPNHYTTT RDLISIMRCA
 201 LKEPPFRGVI STTSYKIGAT NLHGERILSP TNKLLLPGST YHYPPALGGK
 251 TGTTKTAGKN LIMAAEKNNR LLVTIATGYS GPVSDLYQDV IALCETVFNE
 301 PLLRKELVPP SDCLQLEIAN LGKLSCPLPE GLYYDFYASE DREPLSVSFI
 351 AHADAFPIEQ GDLLGHWVFY DDEGKKISSQ PFYAPCRFER TIKPWKLYMK
 401 RVFTSYRTYM SITMLLMYFR IRKHRKYKNL KHYSKI
```

Possible T cell epitope:

156 FMDKLNFFL

Possible B cell epitope:

422 RKHRKYKN

Figure 33: CPN100515

```
  1 MASNPILQIE DLSITLAKQR QQYPIVQSLS FTINEGQTLA IIGESGSGKS
 51 VSAHAILRLL PCPPFSVSGQ VNFQGHNLLT ASRSIQKKII GTEISMIFQN
101 PQASLNPVFT IEQQFREIIH THLALTAEVA KEKMLYALEE TGFHDPRLCL
151 NLYPHQLSGG MLQRICIAMA LLCSPKLLIA DEPTTALDVS VQYQILQLLK
201 TLQKKTGMSL LIITHNMGVV AETADDVLVL YAGRMVECAP AVQMFHNPSH
251 PYTRDLLASR PSLQPQQLGS FNPIPGQPPH YTAFPSGCRY HPRCSKILNR
301 CSAEAPEIYP VREGHKVRVG CMTTNFPQPL IQATSLTKHY YKRSFWFQGK
351 TIASRPVDDV SFSLYSRRAV GLIGESGSGK STLALALAGL LPLTSGFLTF
401 NGTPIKLHSK HGRHQLRSQV RLVFQNPQAS LNPRKTILDS LGHSLLYHKL
451 VPKEKVLATV REYLELVGLS EEYFYRYPHQ LSGGQQQRVS IARALLGVPQ
501 LIICDEIVSA LDLSIQAQIL NMLAELQKKL SLTYLFISHD LAVVRSFCTE
551 VFIMYKGQIV EKGNTKRIFS DPQHPYTRML LNAQLPETPD QRQSKPIFQE
601 YHKDSEESCS TGCYFYNRCP QKQEACKSEI IPNQGDAHHT YRCIH
```

Possible T cell epitope:

59 LLPCPPFSV

Possible B cell epitopes:

18 KQRQQY
587 ETPDQRQSK

Figure 34: CPN100538

```
   1 MPGIEKAATT VAVPQDKSEE EKVKERLTKR ELTCEDLKDN GYTVNFEDIS
  51 ILELLQFVSK ISGTNFVFDS NDLQFNVTIV SHDPTSVDDL STILLQVLKM
 101 HDLKVVEQGN NVLIYRNPHL SKLSTVVTDS SLKETCEAVV VTRVFRLYRR
 151 QPSAAVNIIQ PLLSHDAIVS ASEATRHVII SDIAGNVDKV SDLLAALDCP
 201 GTSVDMTEYE VKYANPAALV SYCQDVLGTL AEDDAFQMFI QPGTNKIFVV
 251 SSPRLANKAE QLLKSLDVPE MAHTLDDPAS TALALGGTGT TSPKSLRFFM
 301 YKLKYQNGEV IANALQDIGY NLYVTTAMDE DFINTLNSIQ WLEVNNSIVI
 351 IGNQGNVDRV IGLLNGLDLP PKQVYIEVLI LDTSLEKSWD FGVQWVALGD
 401 EQSKVAYASG LLNNTGIATP TKATVPPGTP NPGSIPLPTP GQLTGFSDML
 451 NSSSAFGLGI IGNVLSHKGK SFLTLGGLLS ALDQDGDTVI VLNPRIMAQD
 501 TQQASFFVGQ TVPYQTIKYY IQETGTVTQN IDYEDIGVNL VVTSTVAPNN
 551 VVTLQIEQTI SELHSASGSL TPVTDKTYAA TRLQIPDGCF LVMSGHIRDK
 601 TTKVVSGVPL LNSIPLIRGL FSRTIDQRQK RNIMMFIKPK VISSFEEGTR
 651 VTNKEGYRYN WEADEGSMQV APRHAPECQG PPSLQAESDF KIIEIEAQ
```

Possible T cell epitope:

50 SILELLQFV

Possible B cell epitopes:

15 QDKSEEEK
626 DQRQKRN

Figure 35: CPN100557

```
  1 MSRKDNEVSL ARSIFNILSG TFCSRITGIF REIAMATYFG ADPIVAAFWL
 51 GFRTVFFLRK ILGGLILEQA FIPHFEFLRA QSLDRAAFFF RRFSRLIKGS
101 TIIFTLLIEA VLWVFFNNVE EGTYDMILLT MILLPCGIFL MMYNVNGALL
151 HCGNKFFGVG LAPVVVNIIW IFFVIAARHS DPRERIIGLS VALVIGFFFE
201 WLITVPGVWK FLLEAKSPPQ EHDSVRALLA PLSLGILTSS IFQLNLLSDI
251 CLARYVHEIG PLYLMYSLKI YQLPIHLFGF GVFTVLLPAI SRCVQREDHE
301 RGLKLMKFVL TLTMSVMIIM TAGLLLLALP GVRVLYEHGL FPQSAVYAIV
351 RVLRGYGASI IPMALAPLVS VLFYAQRQYA VPLFIGIGTA LANIVLSLVL
401 GRWVLKDVSG ISYATSITAW VQLYFLWYYS SKRLPMYSKL LWESIRRSIK
451 VMGTTMLACM ITLGLNILTQ TTYVIFLNPL TPLAWPLSSI TAQAIAFLSE
501 SCIFLAFLFG FAKLLRVEDL INLASFEYWR GQRGLLQRQH VMQDTQN
```

Possible T cell epitope:

111 VLWVFFNNV

Possible B cell epitopes:

1 MSRKDNE
295 QREDHERG

Figure 36: CPN100622

```
   1 MKTSRNKQCK ITDPLSKSSF FVGALILGKT TILLNATPLS DYFDNQANQL
  51 TTLFPLIDTL TNMTPYSHRA TLFGVRDDTN QDIVLDHQNS IESWFENFSQ
 101 DGGALSCKSL AITNTKNQIL FLNSFAIKRA GAMYVDGNFD LSENHGSIIF
 151 SGNLSFPNAS NFADTCTGGA VLCSKNVTIS KNQGTAYFIN NKAKSSGGAI
 201 QAAIINIKDN TGPCLFFNNA AGGTAGGALF ANACRIENNS QPIYFLNNQS
 251 GLGGAIRVHQ ECILTKNTGS VIFNNNFAME ADISANHSSG GAIYCISCSI
 301 KDNPGIAAFD NNTAARDGGA ICTQSLTIQD SGPVYFTNNQ GTWGGAIMLR
 351 QDGACTLFAD QGDIIFYNNR HFKDTFSNHV SVNCTRNVSL TVGASQGHSA
 401 TFYDPILQRY TIQNSIQKFN PNPEHLGTIL FSSTYIPDTS TSRDDFISHF
 451 RNHIGLYNGT LALEDRAEWK VYKFDQFGGT LRLGSRAVFS TTDEEQSSSS
 501 VGSVININNL AINLPSILGN RVAPKLWIRP TGSSAPYSED NNPIINLSGP
 551 LSLLDDENLD PYDTADLAQP IAEVPLLYLL DVTAKHINTD NFYPEGLNTT
 601 QHYGYQGVWS PYWIETITTS DTSSEDTVNT LHRQLYGDWT PTGYKVNPEN
 651 KGDIALSAFW QSFHNLFATL RYQTQQGQIA PTASGEATRL FVHQNSNNDA
 701 KGFHMEATGY SLGTTSNTAS NHSFGVNFSQ LFSNLYESHS DNSVASHTTT
 751 VALQINNPWL QERFSTSASL AYSYSNHHIK ASGYSGKIQT EGKCYSTTLG
 801 AALSCSLSLQ WRSRPLHFTP FIQAIAVRSN QTAFQESGDK ARKFSVHKPL
 851 YNLTVPLGIQ SAWESKFRLP TYWNIELAYQ PVLYQQNPEI NVSLESSGSS
 901 WLLSGTTLAR NAIAFKGRNQ IFIFPKLSVF LDYQGSVSSS TTTHYLHAGT
 951 TFKF
```

Possible T cell epitope:

119	ILFLNSFAI

Possible B cell epitopes:

2	KTSRNKQ
647	NPENKG
694	QNSNNDAK

Figure 37: CPN100626

```
   1 MQVFPKVTLS LDYSADISSS TLSHYLNVAS RMRFLTISDQ NRKIKEPLVS
  51 KTPPKFLFYL GNFTACMFGM TPAVYSLQTD SLEKFALERD EEFRTSFPLL
 101 DSLSTLTGFS PITTFVGNRH NSSQDIVLSN YKSIDNILLL WTSAGGAVSC
 151 NNFLLSNVED HAFFSKNLAI GTGGAIACQG ACTITKNRGP LIFFSNRGLN
 201 NASTGGETRG GAIACNGDFT ISQNQGTFYF VNNSVNNWGG ALSTNGHCRI
 251 QSNRAPLLFF NNTAPSGGGA LRSENTTISD NTRPIYFKNN CGNNGGAIQT
 301 SVTVAIKNNS GSVIFNNNTA LSGSINSGNG SGGAIYTTNL SIDDNPGTIL
 351 FNNNYCIRDG GAICTQFLTI KNSGHVYFTN NQGNWGGALM LLQDSTCLLF
 401 AEQGNIAFQN NEVFLTTFGR YNAIHCTPNS NLQLGANKGY TTAFFDPIEH
 451 QHPTTNPLIF NPNANHQGTI LFSSAYIPEA SDYENNFISS SKNTSELRNG
 501 VLSIEDRAGW QFYKFTQKGG ILKLGHAASI ATTANSETPS TSVGSQVIIN
 551 NLAINLPSIL AKGKAPTLWI RPLQSSAPFT EDNNPTITLS GPLTLLNEEN
 601 RDPYDSIDLS EPLQNIHLLS LSDVTARHIN TDNFHPESLN ATEHYGYQGI
 651 WSPYWVETIT TTNNASIETA NTLYRALYAN WTPLGYKVNP EYQGDLATTP
 701 LWQSFHTMFS LLRSYNRTGD SDIERPFLEI QGIADGLFVH QNSIPGAPGF
 751 RIQSTGYSLQ ASSETSLHQK ISLGFAQFFT RTKEIGSSNN VSAHNTVSSL
 801 YVELPWFQEA FATSHSLAYG YGDHHLHAYI RHIKNRAEGT CYSHTLAAAI
 851 GCSFPWQQKS YLHLSPFVQA IAIRSHQTAF EEIGDNPRKF VSQKPFYNLT
 901 LPLGIQGKWQ SKFHVPTEWT LELSYQPVLY QQNPQIGVTL LASGGSWDIL
 951 GHNYVRNALG YKVHNQTALF RSLDLFLDYQ GSVSSSTSTH HLQAGSTLKF
```

Possible T cell epitope:

56 FLFYLGNFT

Possible B cell epitopes:

39 DQNRKIK
597 NEENRDPYD

Figure 38: CPN100628

```
   1 MLLPFTFVLA NEGLQLPLET YITLSPEYQA APQVGFTHNQ NQDLAIVGNH
  51 NDFILDYKYY RSNGGALTCK NLLISENIGN VFFEKNVCPN SGGAIYAAQN
 101 CTISKNQNYA FTTNLVSDNP TATAGSLLGG ALFAINCSIT NNLGQGTFVD
 151 NLALNKGGAL YTETNLSIKD NKGPIIIKQN RALNSDSLGG GIYSGNSLNI
 201 EGNSGAIQIT SNSSGSGGGI FSTQTLTISS NKKLIEISEN SAFANNYGSN
 251 FNPGGGGLTT TFCTILNNRE GVLFNNNQSQ SNGGAIHAKS IIIKENGPVY
 301 FLNNTATRGG ALLNLSAGSG NGSFILSADN GDIIFNNNTA SKHALNPPYR
 351 NAIHSTPNMN LQIGARPGYR VLFYDPIEHE LPSSFPILFN FETGHTGTVL
 401 FSGEHVHQNF TDEMNFFSYL RNTSELRQGV LAVEDGAGLA CYKFFQRGGT
 451 LLLGQGAVIT TAGTIPTPSS TPTTVGSTIT LNHIAIDLPS ILSFQAQAPK
 501 IWIYPTKTGS TYTEDSNPTI TISGTLTLRN SNNEDPYDSL DLSHSLEKVP
 551 LLYIVDVAAQ KINSSQLDLS TLNSGEHYGY QGIWSTYWVE TTTITNPTSL
 601 LGANTKHKLL YANWSPLGYR PHPERRGEFI TNALWQSAYT ALAGLHSLSS
 651 WDEEKGHAAS LQGIGLLVHQ KDKNGFKGFR SHMTGYSATT EATSSQSPNF
 701 SLGFAQFFSK AKEHESQNST SSHHYFSGMC IAKYSLQRVI RLSVSLAYMF
 751 TSEHTHTMYQ GLLEGNSQGS FHNHTLAGAL SCVFLPQPHG ESLQIYPFIT
 801 ALAIRGNLAA FQESGDHARE FSLHRPLTDV SLPVGIRASW KNHHRVPLVW
 851 LTEISYRSTL YRQDPELHSK LLISQGTWTT QATPVTYNAL GIKVKNTMQV
 901 FPKVTLSLDY SADISSSTLS HYLNVASRMR F
```

Possible T cell epitope:

1 MLLPFTFVL

Possible B cell epitopes:

38 HNQNQ
619 YRPHPERRG
669 HQKDKNG

Figure 39: CPN100630

```
   1 MPLSFKSSSF CLLACLCSAS CAFAETRLGG NFVPPITNQG EEILLTSDFV
  51 CSNFLGASFS SSFINSSSNL SLLGKGLSLT FTSCQAPTNS NYALLSAAET
 101 LTFKNFSSIN FTGNQSTGLG GLIYGKDIVF QSIKDLIFTT NRVAYSPASV
 151 TTSATPAITT VTTGASALQP TDSLTVENIS QSIKFFGNLA NFGSAISSSP
 201 TAVVKFINNT ATMSFSHNFT SSGGGVIYGG SSLLFENNSG CIIFTANSCV
 251 NSLKGVTPSS GTYALGSGGA ICIPTGTFEL KNNQGKCTFS YNGTPNDAGA
 301 IYAETCNIVG NQGALLLDSN TAARNGGAIC AKVLNIQGRG PIEFSRNRAE
 351 KGGAIFIGPS VGDPAKQTST LTILASEGDI AFQGNMLNTK PGIRNAITVE
 401 AGGEIVSLSA QGGSRLVFYD PITHSLPTTS PSNKDITINA NGASGSVVFT
 451 SKGLSSTELL LPANTTTILL GTVKIASGEL KITDNAVVNV AGFATQGSGQ
 501 LTLGSGGTLG LATPTGAPAA VDFTIGKLAF DPFSFLKRDF VSASVNAGTK
 551 NVTLTGALVL DEHDVTDLYD MVSLQSPVAI PIAVFKGATV TKTGFPDGEI
 601 ATPSHYGYQG KWSYTWSRPL LIPAPDGGFP GGPSPSANTL YAVWNSDTLV
 651 RSTYILDPER YGEIVSNSLW ISFLGNQAFS DILQDVLLID HPGLSITAKA
 701 LGAYVEHTPR QGHEGFSGRY GGYQAALSMN YTDHTTLGLS FGQLYGKTNA
 751 NPYDSRCSEQ MYLLSFFGQF PIVTQKSEAL ISWKAAYGYS KNHLNTTYLR
 801 PDKAPKSQGQ WHNNSYYVLI SAEHPFLNWC LLTRPLAQAW DLSGFISAEF
 851 LGGWQSKFTE TGDLQRSFSR GKGYNVSLPI GCSSQWFTPF KKAPSTLTIK
 901 LAYKPDIYRV NPHNIVTVVS NQESTSISGA NLRRHGLFVQ IHDVVDLTED
 951 TQAFLNYTFD GKNGFTNHRV STGLKSTF
```

Possible T cell epitope:

936 GLFVQIHDV

Possible B cell epitopes:

281 KNNQGK
345 SRNRAEK
707 HTPRQGHE